PIPERIDINE-4-ONE DERIVATIVES : SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL EVALUATION

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Abstract : Piperidine derivatives are an important class of nitrogen-containing heterocycles with diverse pharmacological applications. In this study, piperidine-4-one and its aromatic derivatives were synthesized using the Mannich reaction via the Noller-Baliah method. The compounds were purified by recrystallization and characterized through melting point determination, solubility testing, TLC profiling and IR spectroscopy. Antimicrobial activity was evaluated using the disc diffusion assay. Results revealed that substituted derivatives exhibited stronger inhibition compared to the parent compound, particularly at the 2 and 6 position of the ring. Among them, the nitro-substituted derivative demonstrated the highest activity, comparable to streptomycin. These findings highlights the potential of piperidine-4-one scaffolds as promising candidates for antimicrobial drug development.

Keywords : Piperidine-4-one, Mannich reaction, Antimicrobial activity, Heterocyclic compounds.

1. INTRODUCTION

Medicinal chemistry continues to drive the Discovery of novel therapeutic agents. Piperidine derivatives are widely studied due to their broad biological spectrum, including antimicrobial, analgesic, and anticancer properties. The Mannich reaction remains a classical and efficient route for synthesizing these compounds. Over the last decade, several piperidine derivatives have been reported in preclinical and clinical studies. This work focuses on synthesizing piperidine-4-one derivatives, characterizing their physicochemical properties, and evaluating their antimicrobial potential.

Uses :-

1) The piperidine ring serves as a central pharmacophore in medical chemistry, allowing fine-tuning of properties such as basicity, solubility, and receptor binding across diverse therapeutic areas.

2) Beyond pharmaceuticals, piperidine derivatives find applications in ionic liquids, polymer additives, corrosion inhibitors, and surfactants.

3) Naturally occurring alkaloids like atropine are clinically employed to manage nausea, vomiting, and bradycardia.

4) Piperidine-based compounds such as morphine remain indispensable as analgesics for severe pain relief.

2. REVIEW OF LITERATURE

2.1 Foundations of Piperidine-4-one Chemistry

The study of piperidine-4-one derivatives began with the pioneering work of Noller and Baliah, who demonstrated that the Mannich reaction could reliably produce substituted 4-piperidones in good yield [1]. Their method, involving ketones, aldehydes, and ammonium acetate in acetic acid, became the cornerstone for subsequent synthetic explorations.

2.2 Influence of Substitution on Biological Activity

Kalaiselvan and colleagues highlighted the antimicrobial and analgesic potential of nitroso-substituted derivatives [2], while Ganapathy and Vijayan explored halogenated analogues, showing that chloro and bromo substitutions could significantly alter pharmacological outcomes [3].

2.3 Role of Stereochemistry and Structural Design

Zakrzewski and co-workers studied tetramethyl piperidine derivatives, emphasizing how steric and electronic influences shape pharmacological behaviour [4]. Advances in stereoselective Mannich reactions, reported by Van Rootselaar and others, allowed chemists to access enantiopure piperidine cores [5]. Troin's use of chiral pool strategies [6] and Kunz;s introduction of chiral auxiliaries [7] further demonstrated that asymmetric synthesis could yield naturally occurring alkaloids with high efficiency.

2.4 Modern Synthetic Innovations

Ruan introduced vinylogous Mannich reactions to prepare highly substituted piperidines with improved yields and selectivity [8], while Iza and co-workers employed asymmetric Mannich reaction to generate 2,3-disubstituted derivatives [9]. Gianelli expanded the scope by synthesizing diastereoisomers [10].

2.5 Biological Evaluation and Antimicrobial Potential

Researchers have explored diverse chemical modifications to enhance antimicrobial properties. Perumal and Sivakkumar reported the successful synthesis of 2,6-disubstituted compounds, validating their activity through disc diffusion assays [11]. Kabilan highlighted how stereochemical variations in morpholinoacetyl derivatives directly influenced antimicrobial effectiveness [12]. Joshi underscored the role of infrared (IR) spectral analysis in confirming structural features [13], while Ramalingam advanced recrystallization methods to improve the purity of non-volatile solids [14].

3. AIM AND OBJECTIVES.

Aim : Piperidine-4-one derivatives : Synthesis, characterization, and antimicrobial evaluation.

Objectives :

Previous studies have demonstrated that piperidine-4-one derivatives exhibit diverse pharmacological properties, including antimicrobial, antitubercular, and analgesic activities. Particularly, aromatic substitutions at the 2^{nd} and 6^{th} positions of the piperidine-4-one nucleus have been correlated with enhanced antimicrobial and analgesic effects. The piperidine scaffolds, especially in the form of Mannich bases, is recognized as a potent pharmacodynamic framework with reported antimicrobial and anticancer potential. Building upon our

earlier investigations into piperidine-4-one derivatives, we hypothesize that the incorporation of aromatic aldehyde moieties at the 2nd and 6th positions will yield novel compounds with improved biological activity. The present study is therefore aimed at synthesizing, characterizing, and evaluating such derivatives to explore their therapeutic relevance.

4. CHEMICAL STRUCTURE :-

1) Piperidine-4-one

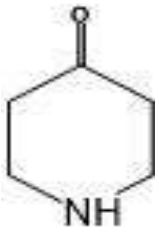


Fig.no 1. Piperidine-4-one

Fig.no 2. 3d structure of piperidine-4-one

2) 2(p-chlorobenzyl)6(p-bromobenzyl)Ppiperidine-4-one

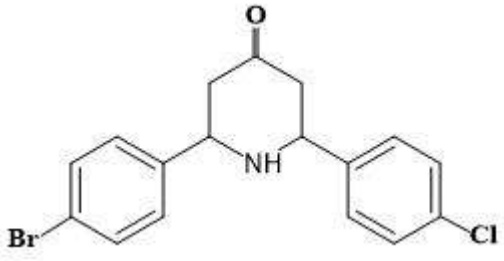


Fig.no 3. 2(p-chlorobenzyl)6(p-bromobenzyl)Piperidine-4-one

Fig.no 4. 3d structure of 2(p-chlorobenzyl)6(p-bromobenzyl)piperidine-4-one

3) 2(p-bromophenyl) (6-phenyl) piperidine-4-one

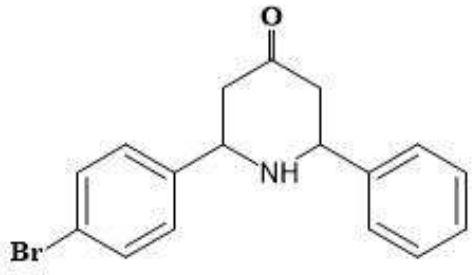


Fig.no 5. 2(p-bromophenyl) (6-phenyl) piperidine-4-one

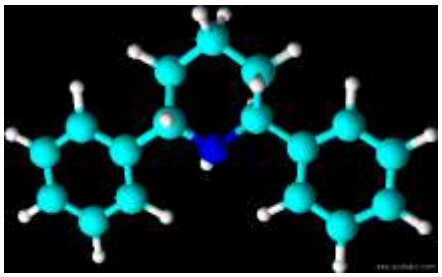


Fig.no 6. 2(p-bromophenyl (6-phenyl) piperidine-4-one

4) 2(2-bromophenyl) (6-phenyl)piperidine-4-one

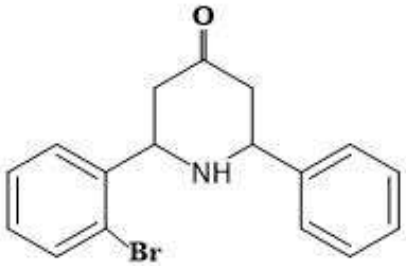


Fig.no 7. 2(2-bromophenyl) (6-phenyl)piperidine-4-one

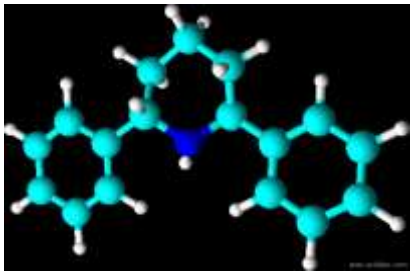


Fig.no 8. 3d structure of 2(2-bromophenyl) (6-phenyl)piperidine-4-one

5) 2(p-nitrophenyl) (6-phenyl)piperidine-4-one

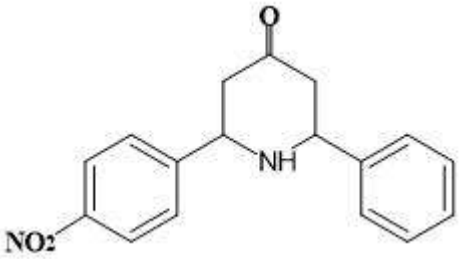


Fig.no 9. 2(p-nitrophenyl) (6-phenyl)piperidine-4-one

Fig.no 10. 2(p-nitrophenyl) (6-phenyl)piperidine-4-one

5. METHODOLOGY

The synthesis was carried out using Noller-Baliah protocol, where acetone, ammonium acetate, and substituted benzaldehydes were condensed in glacial acetic acid. Products were purified by recrystallization in ethanol.

The melting points were checked by open capillary tube method. The spectra of IR of the compounds were recorded using Perkin-Elmer FT-IR spectrometer. The purity of the compounds were determined using TLC on pre-coated SiO_2 gel (HF254 200 mesh) Aluminium plates (E-merk) using ethyl acetate : n-hexane as eluent.The IR, consistent with the assigned structure.

Fig.no 11. MP Instrument

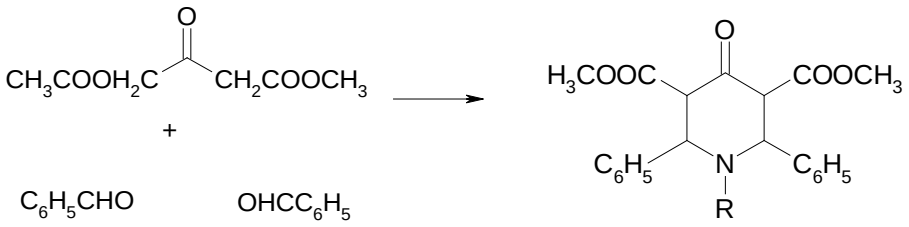
Fig.no 12. IR Instrument

Fig.no. 13. TLC

5.1 Synthetic Method

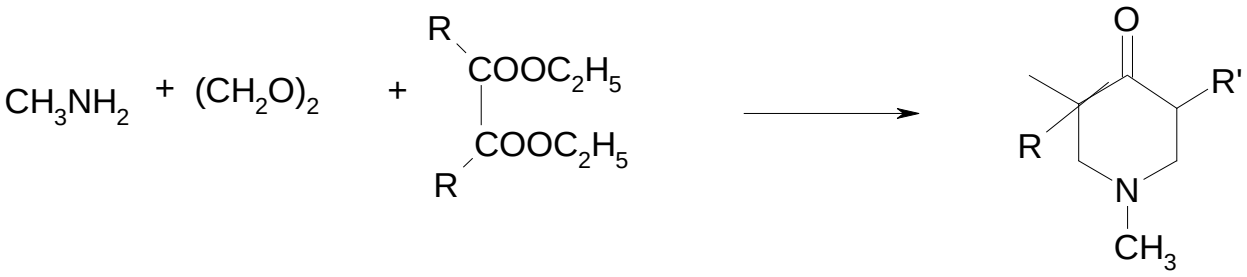
➢ General procedure for piperidine-4-one

The preparation of piperidone derivatives has been explored through sseveral classical approaches. One of the earliest methods, developed by Petrenko-Kritscenko, involves the condensation of two molecules of benzaldehyde with ammonia (or a primary amine) and an ester of acetone dicarboxylic acid.

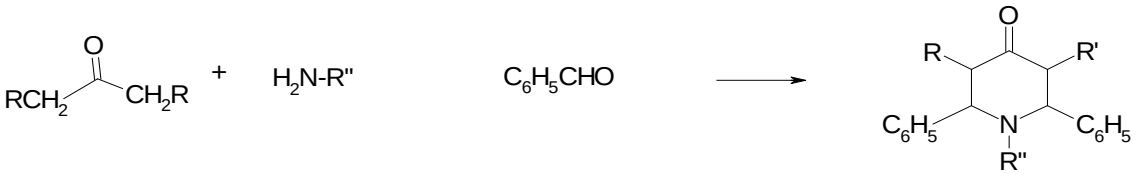


This pathway proved versatile, with aceataldehyde successfully replacing benzaldehyde to give a 46% yeild, although attempts with formaldehyde were largely unsuccessful.

Interestingly, ethyl α,α′-diethylacetone dicarboxylate reacts with formaldehyde and methylamine to furnish a piperidone, as the two active hydrogens in the 1,3-position minimize side reaction and improve yield. In certain cases, further condensation with formaldehyde and methylamine produces bicyclic pyridines known as bispidines.



Subsequent efforts to adapt this reaction to simple ketones were initially unsatisfactory. However, Baliah later demonstrated that the process proceeds smoothly when acetic acid is employed as the solvent, significantly improving reproducibility.



The yields were highest when ammonia was used (R=H), while bulkier substituents on the amine reduced efficiency. On the other hand, benzaldehyde could be readily substituted with other aromatic aldehydes such as anisaldehyde, piperonol, and veratraldehyde without substantial loss in yield. These refinements established the Mannich-type condensation as a reliable route for synthesizing piperidones and their derivatives, laying the foundation for further medicinal chemistry applications.

➢ **Synthesis of piperidine-4-one derivatives.**

Synthesis of piepridine-4-one derivatives was carried out following classical method reported by Noller and Baliah. In this approach, acetone, dry ammonium acetate, and two equivalents of substituted benzaldehyde were combined in glacial acetic acid gently heated to maintain a simmer. Reaction mixture was then allowed to stand at room temperature for 12-14 hours to ensure complete condensation.

After this period, toluene was introduced, followed by concentrated hydrochloric acid, and the mixture was cooled in an ice bath. The resulting hydrochloride salt was collected by filtration, washed with an ethanol-ether mixture, and transferred to a large vessel. To libertate the freebase, the salt was suspended in acetone and carefully treated with concentrated ammonia solution. Dilution with excess water facilitated precipitation of the crude piperidone, which was isolated by filtration, throughly wash out with water, and dried. Finally, the product was purified by recrystallization from absolute ethanol, yielding crystalline piperidine-4-one derivatives suitable for further characterization.

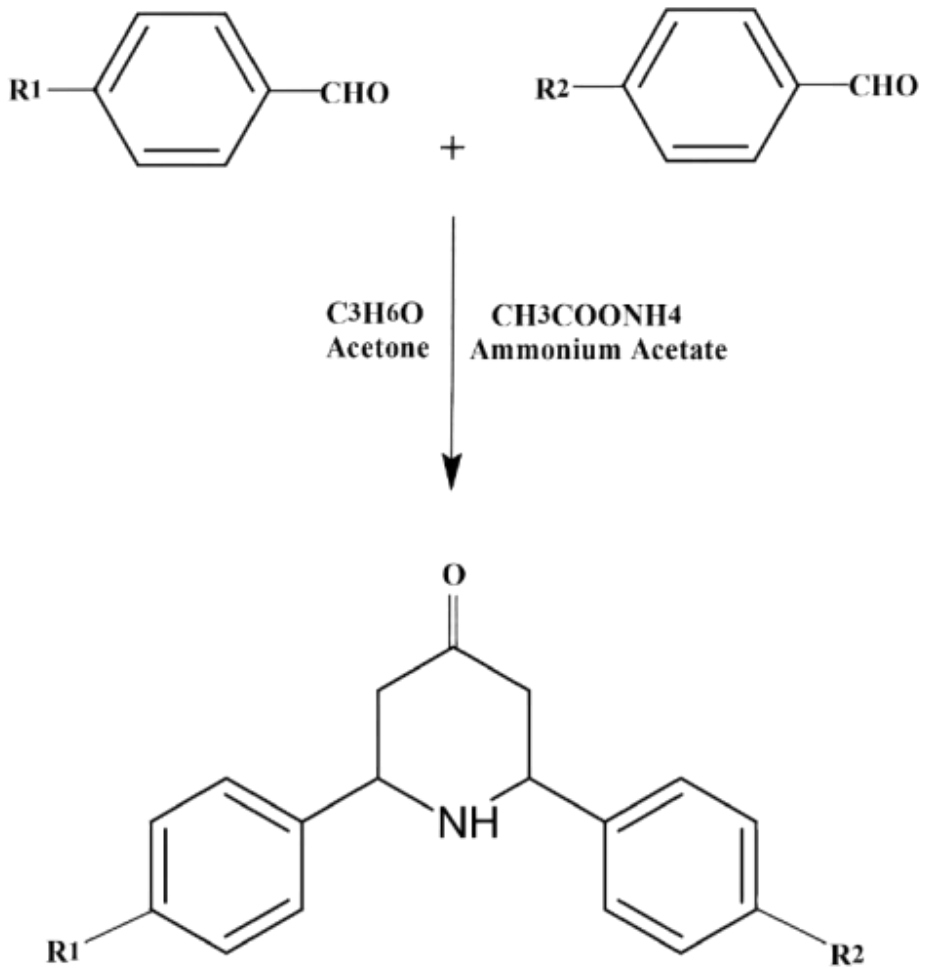


Fig.no 14. General procedure for synthesis of piperidine-4-one derivatives

➢ **Synthesis of 2(p-chlorobenzyl) 6(p-bromobenzyl) piperidine-4-one**

The chloro-bromo derivative of piperidone was synthesized using the Noller-Baliah protocol. Acetone, dry ammonium acetate, p-chlorobenzaldehyde, and p-bromobenzaldehyde were dissolved in glacial acetic acid and gently heated to 12-14 hours. After completion, toluene and Concentrated hydrochloric acid were added, and the solution was cooled in an ice bath. The resulting hydrochloride salt was filtered out, washed with an ethanol-ether mixture, and suspended in acetone. Basification with concentrated ammonia liberated the free base, which precipitated upon dilution with water.

At the end crude product was collected, washed throughly, dried, and recrystallized from absolute ethanol to yeild the purified chloro-bromo piperidone derivative.

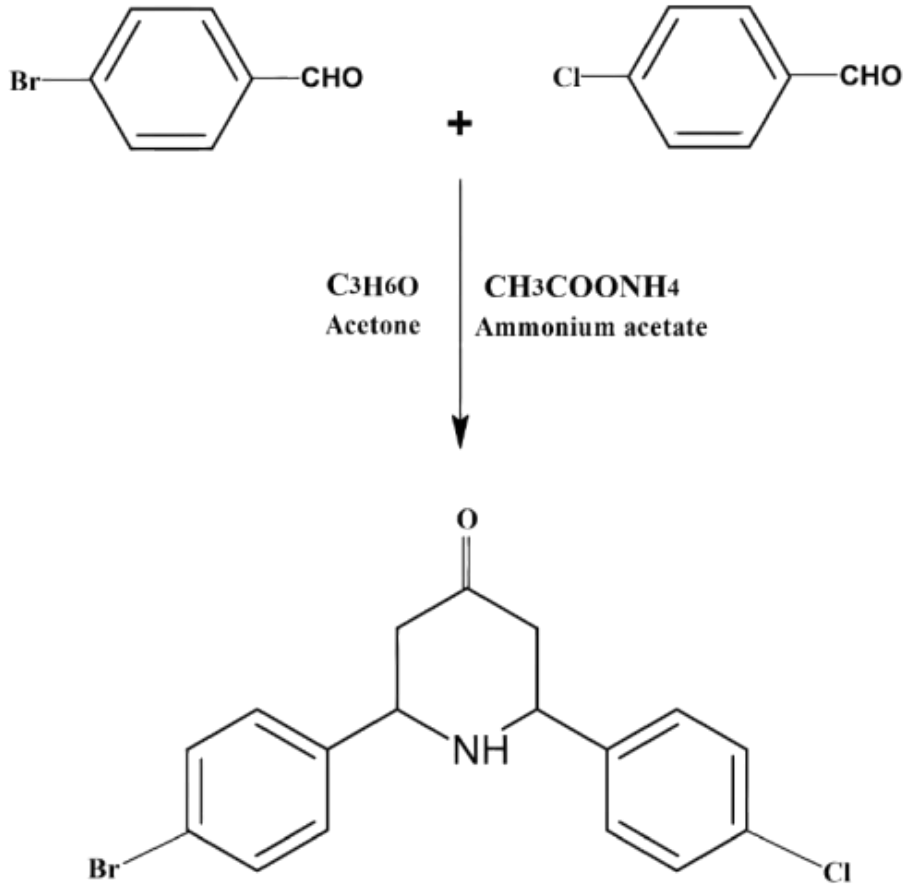


Fig.no 15. Synthesis of 2(p-Chlorobenzyl) 6(p-bromobenzyl) piperidine-4-one

➢

➢ **Synthesis of 2(p-bromophenyl) (6-phenyl) piperidine-4-one.**

A mixture of acetone, dry ammonium actate, p-bromobenzaldehyde, and benzaldehyde was condensed in glacial acetic acid under gentle heating. The reaction mixture was allowed to stand for 12-14 hours, then treated with toluene and concentrated hydrochloric acid. Cooling produced the hydrochloride salt, which was isolated by filtration. Basification with ammonia released the free base, and recrystallization from ethanol afforded the pure p-bromo derivatives.

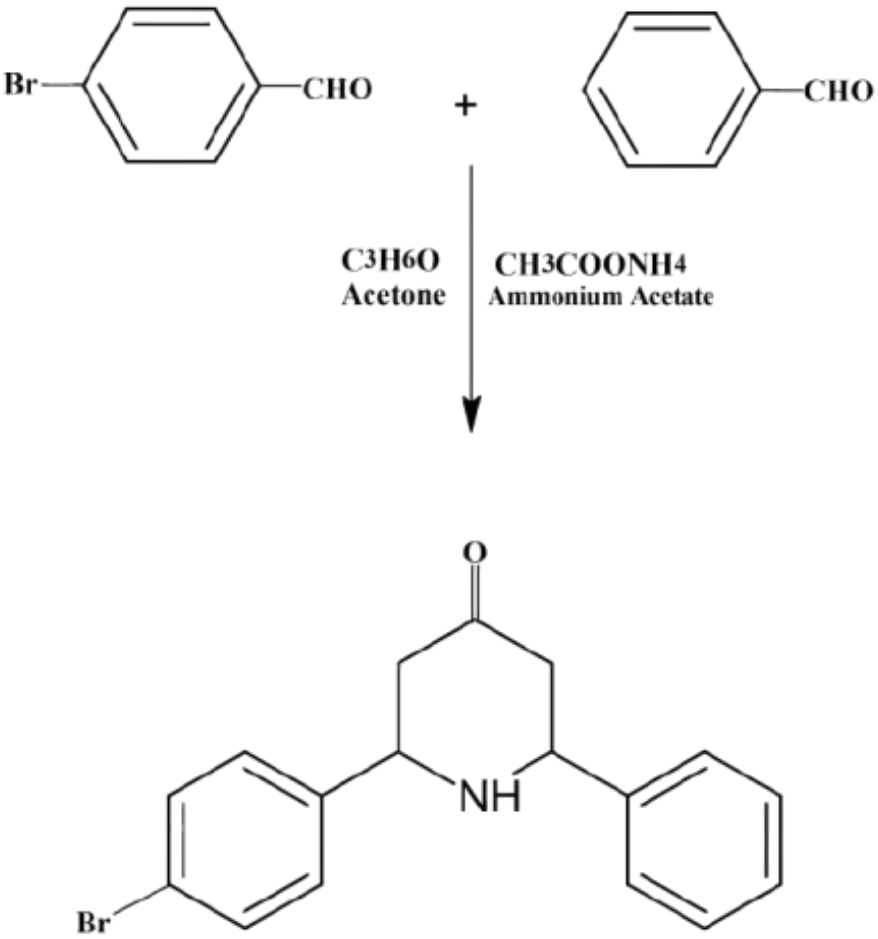


Fig.no 16. Synthesis of 2(p-bromophenyl) (6-phenyl) piperidine-4-one

➢ **Synthesis of 2(2-bromophenyl) (6-phenyl) piperidine-4-one**

A mixture of acetone, dry ammonium acetate, 2-bromobenzaldehyde, and benzaldehyde was condensed in glacial acetic acid under gentle heating. The reaction mixture was allowed to stand or 12-14 hours, then treated with toluene and concentrated hydrochloride acid. Cooling produced the hydrochloride salt, which was isolated by filtration. Basification with ammonia released the free base, and recrystallizaton from ethanol afforded the pure 2-bromo derivative.

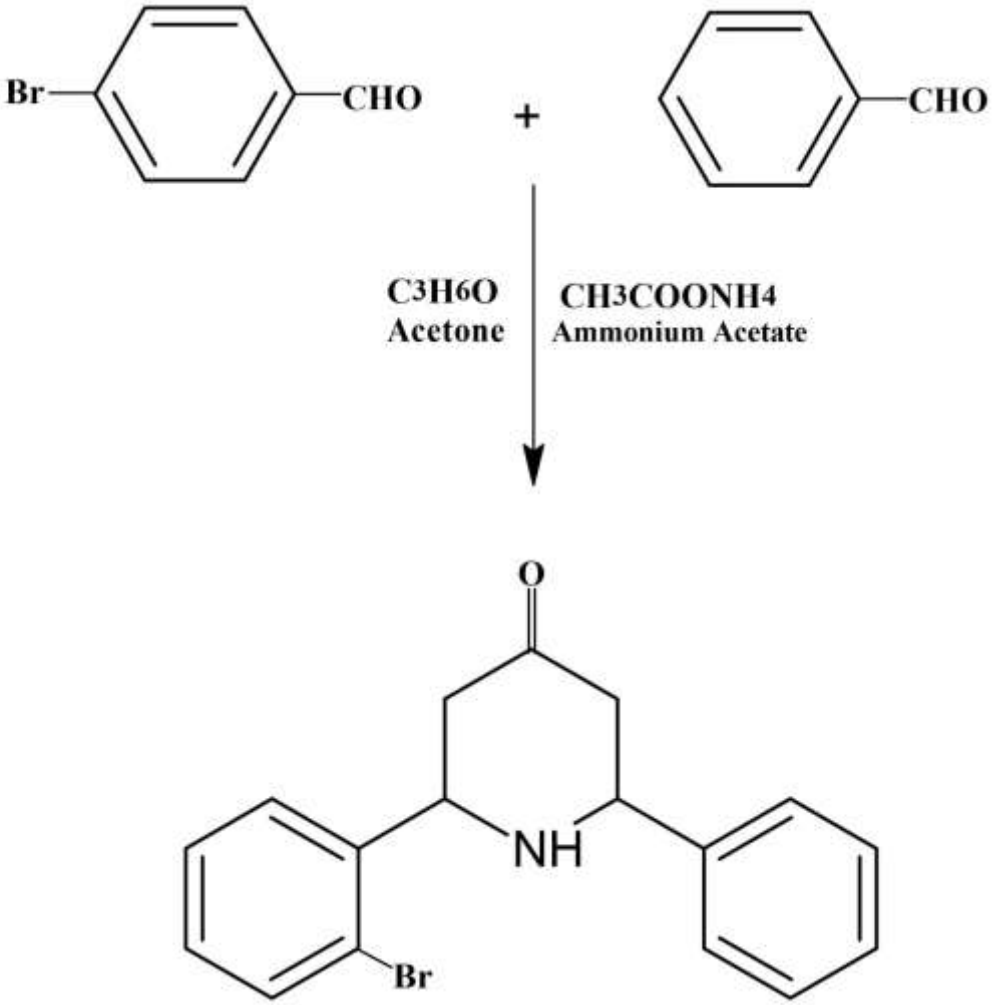


Fig.no 17. Synthesis of 2(2-bromophenyl) (6-phenyl) piperidine-4-one

➢ Synthsis of 2(p-nitrophenyl) (6-phenyl) piperidine-4-one

The nitro substituted deivatives was prepared by Condensing acetone, dry ammonium acetate, p-nitrobenzaldehyde, and benzaldehyde in glacial acetic acid. The mixture was gently heated and then left at room temperature for 12-14 hours. Subsequent addition of toluene and concentrated hydrochloride acid, followed by Cooling, produced the hydrochloride salt. This was filtered, washed, and suspended in acetone. Basification with ammonia liberated the free base, which was precipitated, washed, dried, and recrystallized from ethanol to obtain the pure nitro-piperidine derivative.

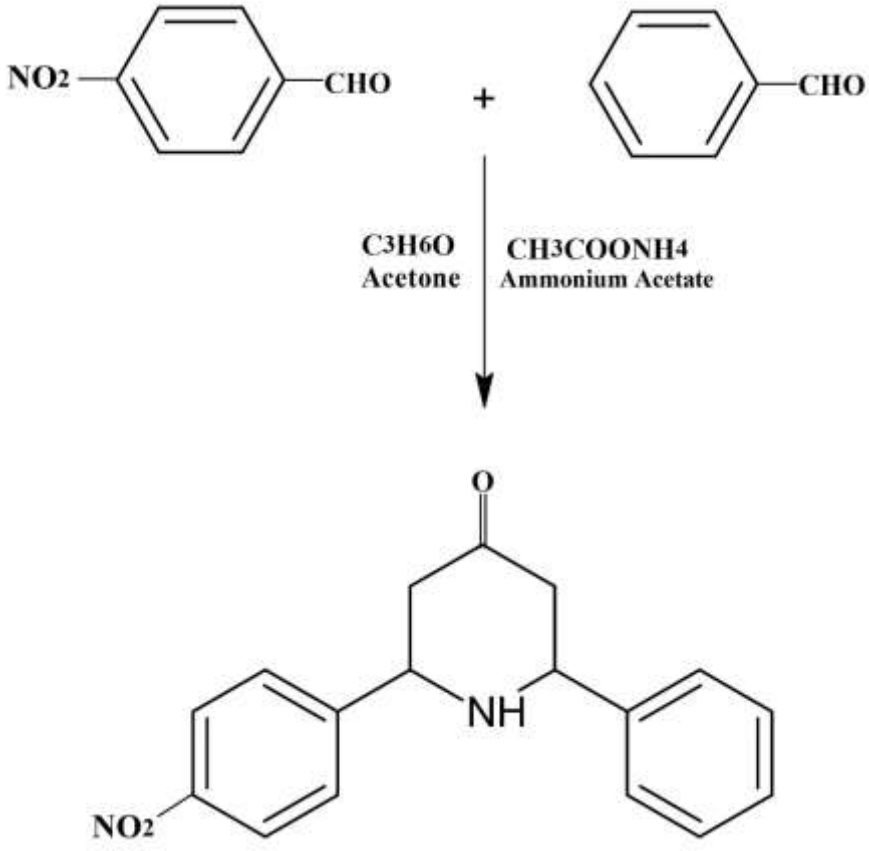


Fig.no 18. 2(p-nitrophenyl) (6-phenyl) piperidine-4-one

6. Physicochemical properties :-

Compound name	Formula	Molecular weight	Melting point	Solubility	TLC
Piperidine-4-one	C9H9NO	99.13g/mol	~ 28.30 °C	Soluble in Water, Acetone, Ethanol And Insoluble in Methane, Ethyl Acetate, Glacial acetic acid.	0.40
2(p-chlorobenzyl)6(p-bromobenzyl)piperidine-4-one	C19H23BRCINO	396.7 g/mol	~ 140-180 °C	Soluble in Water, Acetone, Ethanol And Insoluble in Methane, Ethyl Acetate, Glacial acetic acid.	0.71
2(p-bromophenyl) (6-phenyl)piperidine-4-one	C17H16BrNO	330.22 g/mol	~ 120-125 °C	Soluble in Water, Acetone, Ethanol And Insoluble in Methane, Ethyl Acetate, Glacial acetic acid.	0.533

2(2-bromophenyl) (6-phenyl) piperidine-4-one	C17H16BrNO	330.22 g/mol	~ 120-125 °C	Soluble in Water, Acetone, Ethanol And Insoluble in Methane, Ethyl Acetate, Glacial acetic acid.	0.42
2(p-nitrophenyl) (6-phenyl) piperidine-4-one	C17H16N2O3	296.32 g/mol	~ 150- 160 °C	Soluble in Water, Acetone, Ethanol And Insoluble in Methane, Ethyl Acetate, Glacial acetic acid.	0.4

Table.no 1. Physicochemical properties of Compounds

7. CHARACTERISATION OF COMPOUND.

7.1 IR analysis of synthesized compound.

Compound	N-H / C-H Stretching	C-H Stretching	C=O Stretching	Other key bands
2(p-chlorobenzyl)6(p bromobenzyl) piperidine-4-one	3116 , 3011 cm^{-1}	3000, 2850 cm^{-1}	1648 cm^{-1}	C-Br : 650, 500 cm^{-1} C-Cl : 850,550 cm^{-1} C-N : 1325,1190 cm^{-1}
2-(2bromophenyl)piperidine-4-one	3116, 3011 cm^{-1}	2802 cm^{-1}	1736 cm^{-1}	C-Br : 689 cm^{-1} C-N :1442 cm^{-1}
2-(p-nitrophenyl)piperidine-4-one	3108, 3041 cm^{-1}	2948, 2847 cm^{-1}	1733 cm^{-1}	NO_2 Stretching : 1341 cm^{-1} C-N : 1192, 1073cm^{-1} NO_2 Bending : 805 cm^{-1}

Table.no 2. IR analysis data of synthesized compound

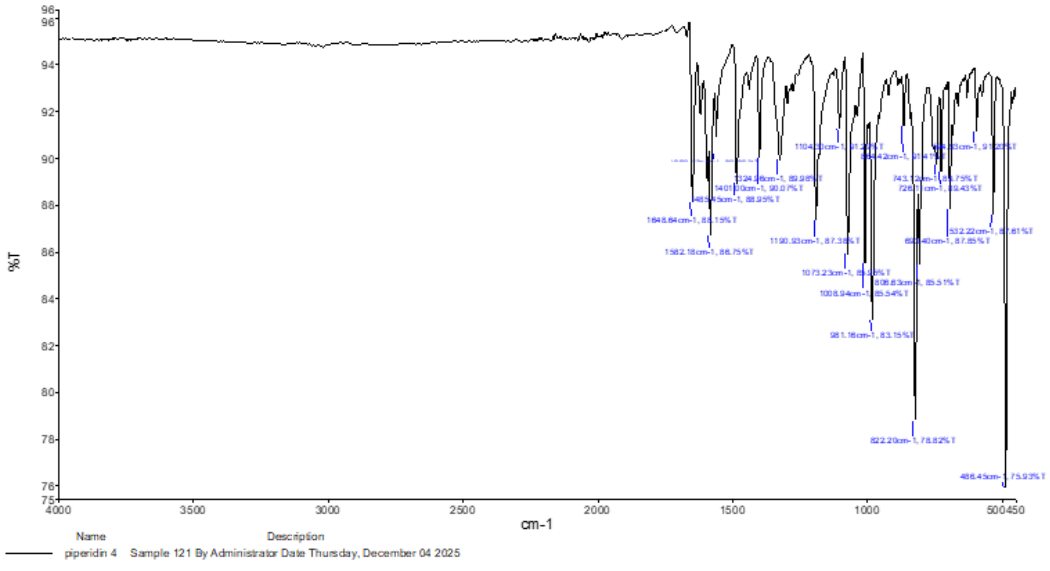


Fig.no 19. IR analysis of 2(p-chlorobenzyl)-6-(p-bromobenzyl) piperidine-4-one

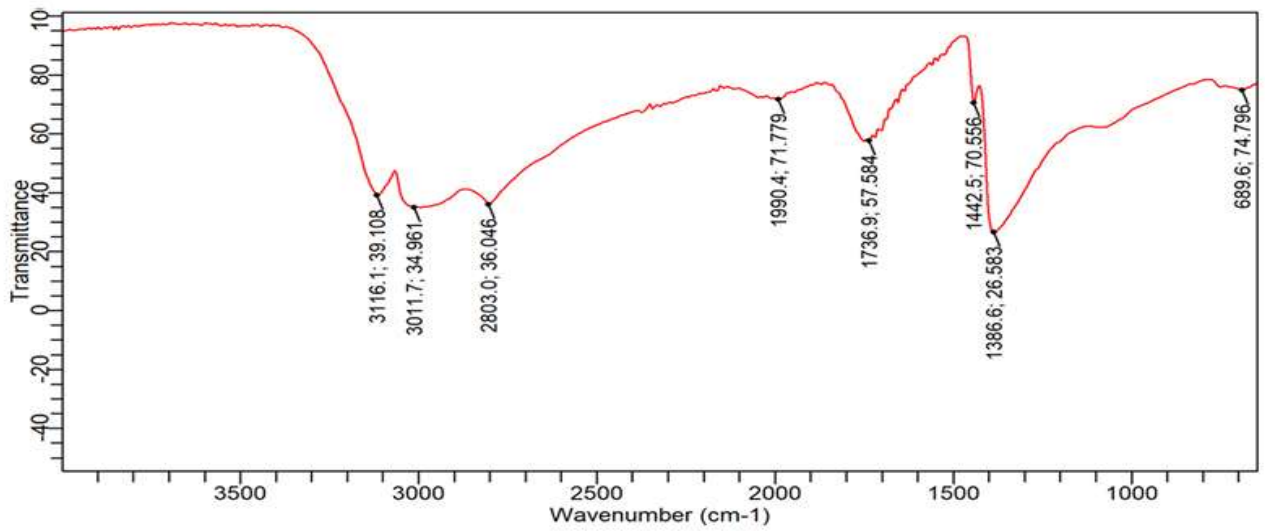


Fig.no 20. IR analysis of 2(2-bromophenyl)-(6-phenyl) piperidine-4-one

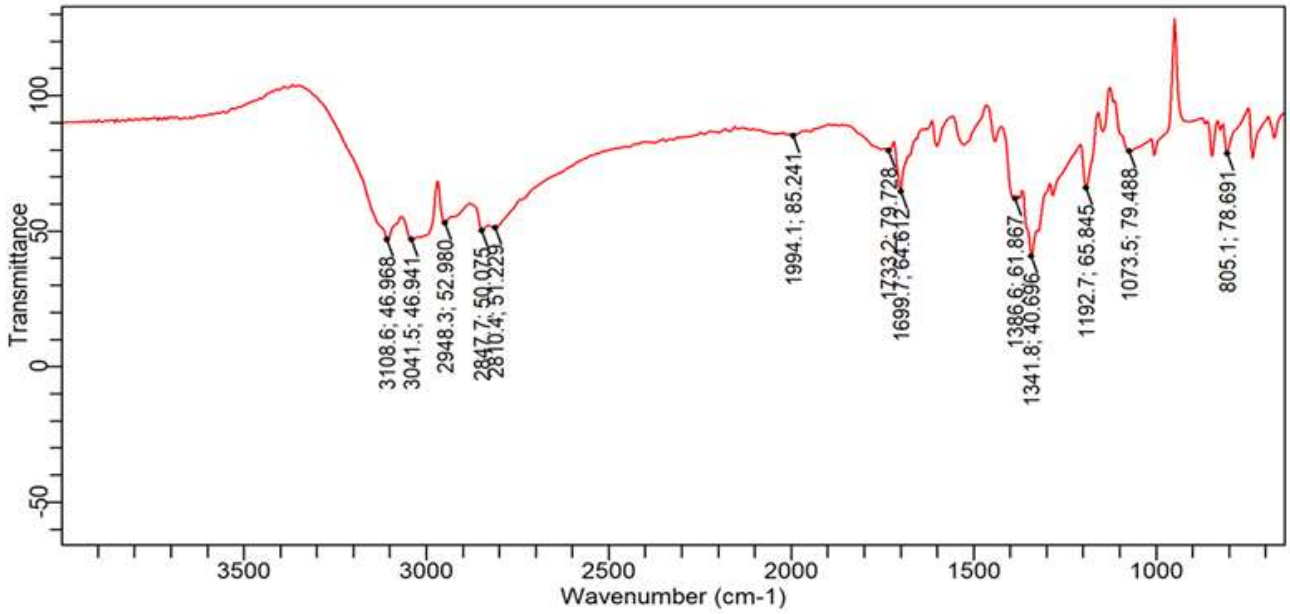


Fig.no 21. IR analysis of 2(p-nitrophenyl)-(6-phenyl) piperidine-4-one

Fig.no 22.Piperidne-4-one

Fig.no 23. Compound 1

Fig.no 24. compound 2

Fig.no 25. Compound 3

Fig.no 26. compound 4

Fig.no 27. Determination of MP

Fig.no 28. Determination of TLC

Fig.no 29. Determination of Solubility

Fig.no 30. Research Activities: Piperidine-4-one and Its Derivatives

8. Evaluation of Compound.

6.1 Antimicrobial study of Compound

Material and Methods :
Disc diffusion assay

The antimicrobial properties of the synthesized compounds were investigated using the Kirby-Bauer disc diffusion technique. Sterile paper discs (Himedia Pvt. Ltd. Mumbai) were treated with 50 ul of each test solution at a concentrated of 1mg/ml and subsequently dried before use These prepared discs were carefully placed on agar plates that had been seeded with 24-hours-old microbial cultures. For comparison, standard antibiotic discs of the same concentration were included as controls. The plates were incubated at 37 °C for 24-28 hours, after which the diameters of the inhibition zones were measured with a Himedia zone scale. All experiments ere performed in triplicate, and the data were expressed as mean values accompanied by standard deviation to ensure reliability.

Statistical analysis :

All the experiments were done in triplicate and the values are calculated by applying Standard Deviation (± SD)

Result of Antimicrobial activity

Disc diffusion assay

The results of the disc diffusion assay are summarized in table.no 3. Among the tested compounds, the nitro derivatives (CB-2) demonstrated the most pronounced inhibitory activity against the selected bacterial strains, showing strong effects against *E. coli.*

Compounds	Bacterial Strains		
	E. coli	***S. aureus***	***P. aerugenosa***
CB1 Compound 1 (Chloro and Bromo derivative)	+	+	+
CB2 Compound 4 (Nitro derivative)	+++	+++	++++
Streptomycin	+++	+++	+++

Table.no. 3 Antimicrobial activity of synthesized compound against selected pathogen

(+ = < 5mm, ++ = > 5 and < 10 mm, +++ = > 10 and < 18 mm, NZ = No zone, NA = Not applicable Results are the average mean of three parallel experiments)

9. RESULT, OUTCOME, AND CONCLUSION.

Result :-

The synthesized piperidine-4-one derivatives were successfully obtained using the Noller and Baliah method. Each compound was purified and characterized through melting point determination, solubility testing, TLC profiling and IR spectroscopy. The data confirmed the expected structures and purity of the compounds. Antimicrobial evaluation using the disc diffusion method revealed that all derivatives displayed measurable activity against selected bacterial strains. Among them, the nitro-substituted derivative (CB_2) showed the strongest inhibition zones, comparable to the standard drug streptomycin, while the parent compound exhibited only mild activity.

Outcomes :-

- Successfully synthesized piperidine-4-one and its halogen derivatives using the Mannich reaction, reaffirming the reliability of this classical method.

- Confirmed the purity and structural identity of the compound through melting point analysis, solubility studies, TLC profiling, IR spectroscopy.

- Showed the substitution at the 2^{nd} and 6^{th} position produced clear changes in physiochemical properties and biological activity, demonstrating the impact of structural modifications.

- Established antimicrobial activity of the derivatives, validating their pharmacological relevance and potential as bioactive agents.

- Demonstrated the economic advantages of substituting acetone for diethyl ketone, lowering production costs while maintaining compound quality and efficacy.

- Adopted a more environmental favourable synthetic route, aligning the work with sustainable pharmaceutical practices.

Conclusion :-

This study demonstrates that piperidine-4-one derivatives can be efficiently synthesized and characterized through the Mannich reaction, confirming its reliability in heterocyclic chemistry. Structural modification with halogen and nitro groups at key positions enhanced both physicochemical and biological properties, understanding the versatility of the piperidine nucleus in drug design. Importantly, replacing diethyl ketone with acetone simplified the process, reduced costs, and offered an eco-friendly alternative without compromising purity or antimicrobial activity. Overall, these findings highlights piperidine-4-one derivatives as promising scaffolds for

antimicrobial drug development and as valuable starting points for next-generation therapeutic research.

10. ACKNOWLEDGEMENT

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Finally, we express appreciation to the International Journal of Novel Research and Development (IJNRD) for providing an esteemed platform to share and disseminate this research work. The opportunity to contribute to such a reputed journal has been truly encouraging and motivating.

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