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Synthesis, Characterization and Antimicrobial Activities of N-(4-Chlorophenyl)-4-Oxo-2, 6-Diphenylpiperidine-3-Carboxamide Compound

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Abstract: Mannich bases are important class of organic compounds usually obtained by the condensation reaction between an amine, a compound with active hydrogens and an aldehyde. These are versatile intermediates in organic synthesis, and those compounds containing this motif find applications in pharmaceutical, agrochemical, and even material fields since they are widely known for their wide range of biological activities, including antimicrobial properties. Mannich bases containing compounds, particularly centered on those exhibiting antifungal properties. The reactions were carried out with equimolar amounts of the reactants in benzene at 60-70°C for 4–5 h, and the yields ranged from 68 to 80%. The synthesized compounds were characterized by physical constants, IR, ^{1}H and ^{13}C NMR, and mass spectra, and elemental analyses. Their antimicrobial activity was evaluated against gram-positive and gram-negative bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*). The results of antimicrobial screening made it possible to recommend the obtained Mannich bases for the design of new antimicrobial agents. Thus, as part of our interest in antifungal agents, this review aimed to gather information from the literature on the synthesis of various representative. The antifungal effect exhibited by Mannich bases of the heterocycles suggests that compounds that have a heterocyclic system attached to the β-amino core are attractive alternatives oriented to the synthesis of novel and helpful antimicrobial agents.

Keywords: Mannich bases, Antimicrobial, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*

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Introduction

Mannich bases are an important group of compounds in medicinal chemistry. They are generally produced by Mannich reaction, which are carbon-carbon bond forming reactions by the reaction of the multicomponents. These are versatile intermediates of organic synthesis, and those compounds containing this motif find applications in pharmaceutical, agrochemical, and even material fields. Since they are widely known for their wide range of biological activities, including antimicrobial properties. The classical Mannich reaction is the condensation reaction between aldehyde, ketone having α-CH acidic proton/s, and a primary or secondary amines (Chang *et al*., 2024). Mannich reactions are also known as aminomethylation or aminoalkylation reactions (He *et al*., 2023). Although primary amines and even ammonia may be employed as an amine reagent, secondary aliphatic amines (R_2NH) are more commonly encountered as an amine reagent in the Mannich reactions (Mukhlif and Al-Mudhafar, 2023). Mannich reactions need activating group. The carbonyl function in ketones, the phenolic hydroxy in phenols, the terminal carbone carbon triple bond in alkynes, the heteroatom in heterocycles etc. are common examples of pairs of activating groups (Quiroga, and Coy-Barrera, 2023). Aminomethylated drugs could be used to improve the distribution of a drug into the human body. Preparation of the Mannich bases of a drug may increase the hydrophilic properties of drugs through the introduction of a polar function into its chemical structure (Salimova *et al*., 2023). Mannich bases could act as prodrugs which release the active substance under controlled hydrolytic conditions via deamination process (Guchhait Salimova *et al*., 2022).

Mannich reaction is one of such reactions utilized in the synthesis of organic compounds. It consists of the condensation of ammonia or primary or secondary amine, with an aldehyde and a compound containing an active hydrogen atom (Nguyen *et al*., 2023). Mannich reaction has been employed with a wide variety of amine, aldehydes such as formaldehyde, benzaldehyde, acetaldehyde, phenyl acetaldehyde and many others. Compounds that contain active hydrogen which have been employed include ketones, esters, aldehydes, ketones, acetylenes, phenols and certain other with the hydrogen atom of usual activity (Kunz and Pfrengle, 1989). Mannich base derivatives with bridge N-atom have been found to be potent drug in medicinal science and possess wide range of biological activities like antimicrobial (Kunz and Pfrengle, 1989). The Mannich reaction allows the formation of a C–C single bond with the involvement of an aldehyde, an amine and a compound possessing a particularly active hydrogen (Mistry *et al*., 2016). The essence of the Mannich reaction is that the active H is replaced with an aminomethylene group—if formaldehyde (CH_2O) is the aldehyde component—or substituted aminoalkyl moiety—if any other aldehyde is applied (Kamiński *et al*., 2013). Because Mannich bases may be regarded as derivatives of the substrate obtained through substitution by an aminoalkyl moiety, Mannich reactions are also known as aminoalkylation reactions. In the particular instance when formaldehyde is employed as aldehyde component, the substrate is converted into the corresponding Mannich base through an aminomethylation process (Malinka *et al*., 2001). Although primary amines and even ammonia (in the form of an ammonium salt) may be employed as amine reagents in aminomethylations or aminoalkylations, secondary aliphatic amines (R_2NH) are the most commonly encountered as amine reagents in the Mannich reaction (Kanchana *et al*., 2014). As formaldehyde is used to a great extent as aldehyde component in the Mannich reaction, the structural diversity of Mannich bases stems primarily from the miscellaneous types of the substrates that can be subjected to aminomethylation, and secondarily from the variety of amine reagents that can be potentially employed in the Mannich reaction (Kucukoglu, 2014).

Various articles have discussed the Manich bases. van Rootselaar *et al*. (2014) synthesized the stereoselective mannich reactions in the of

enantiopure piperidine alkaloids and derivatives. Andersson *et al.* (2011) synthesized the asymmetric synthesis of prepared piperidines using the nitro-mannich reaction. Hozien *et al.* (2020) synthesized the schiff and mannich bases of new s-triazole derivatives and their potential applications for removal of heavy metals from aqueous solution and as antimicrobial agents. Manap (2022) evaluated *in vitro* antioxidant and antimicrobial activities of novel 3-alkyl (aryl)-4-(3- methoxy- 4- (2-furylcarbonyloxy)-benzyliden-amino)-4, 5-dihydro-1 H-1, 2, 4-triazol-5-ones, and their N-acetyl, N-Mannich base derivatives. Tikhov and Kuznetsov (2020) constructed the piperidine-2, 4-dione-type azaheterocycles and their application in modern drug development and natural product synthesis. Garcia *et al.*(2022) synthesized the leveraging the 1, 3-azadiene-anhydride reaction for the synthesis of functionalized piperidines bearing up to five contiguous stereocenters. Lisnyak *et al*. (2018) prepared the mannich-type reactions of cyclic nitrones effective methods for the enantio-selective synthesis of piperidine- containing alkaloids.

In the present study Mannich bases containing compounds were evaluated for their anti-microbial activity was evaluated against gram-positive and gram-negative bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*).

Materials and Methods

Ammonium formate was taken in vacuum desiccator and dried in the succession pump with half an hour, pressure was released and ammonium formate was dried. Ammonium formate. benzaldehyde and 3-choloroaceto-acetanilide were taken in a RB flask containing ethanol (10 ml). The mixture was refluxed at 70-80ºC in a water bath with shaking until the colour was changed to red orange. The solution was cooled, then 50 ml of ether was added and filtered the solution by common method. Then the filtered solution was transferred into conical flask, 5 ml of conc. HCl was added. White precipitate was formed. The precipitate was washed with 5:1 ethanol ether to dissolved the impure precipitate. White precipitate was formed and dried with succession pump and 10 ml acetone, 5 ml liq. Ammonia and excess of cold water was added. White precipitate was formed and filtered with succession pump and dried. The product was obtained. Then the product was recrystallized with ethanol and the crystal form of product was dried. The melting point of compound was 224-226°C.

Results and Discussion

FT-IR data of compound N-(4-chlorophenyl)-4-oxo-2,6-diphenylpiperidine-3-carboxamide:

The formation of the compound N-(4-chlorophenyl)-4-oxo-2,6-diphenylpiperidine-3-carboxamide were realized by the correlation of IR data with parent compound nitro benzene (Kalluraya *et al.*, 2012). To some extent, the unique infrared wavelengths helped to clarify the compound's structure and piperidine ring. The important FT-IR data collected from the spectrum are given in Table 1.

The literature value was found to be 3100-3000 cm^{-1}. The absorption bands at 1476 and 1462 cm^{-1} are due to aromatic C=-=-C. The absorption band at 746 cm^{-1} is a proof for the presence of C-Cl (Raman and Ravichandran, 2005).

^{1}H NMR spectral data of N-(3-chlorophenyl)-4-oxo-2,6-diphenylpiperidine-3-carboxamide:

The N-H (2° amide) proton is associated with the chemical shift value of 8.05 ppm (Table 2). Associated with aromatic protons is the multiplet at δ 7.53-7.03. For the benzylic protons at C2, the doublet at δ 4.60–4.50 is assigned. The Benzylic proton at C6 is attributed to the signal at δ 4.11-4.06 (Rahmatpour *et al.*, 2019). The methine proton at C3 is responsible for the peak that may be seen as a doublet at δ 3.85–3.81 (Vettukattil *et al.*, 2021). The chemical shift value of δ 2.78-2.80 ppm is attributed to the protons of methylene at C5. The cyclic ring's N-H proton is responsible for a singlet at δ 1.95 (Sharma and Singh, 2019).

Table 1: Assignment of the frequencies was made on the basis of the literature values

GROUP	STRETCHING FREQUENCY (Cm^{-1})
N-H	3338
Aromatic C-H	3020
C=O	1728
C=O	1678
C = = = C	1476, 1462
C-N	1566
C-Cl	746

Table 2: The ^{1}H NMR spectral data of compound N-(3-chlorophenyl)-4-oxo-2,6-diphenylpiperidine-3-carboxamide

Chemical Shift (ppm)	Nature of the Peak	Nature of Protons	Assignment
8.05	singlet	1	N-H Proton (2° amide)
7.53-7.03	multiplet	15	Aromatic protons
4.60-4.50	doublet	1	Benzylic proton at C_2
4.11-4.06	doublet	1	Benzylic proton at C_6
3.85-3.81	Doublet	1	Methine proton at C_3
2.78-2.75	Doublet	1	Methylene proton at C_5
1.95	singlet	1	N – H proton at ring

The ^{13}C NMR Spectral data of compound N-(3-chlorophenyl)-4-oxo-2,6-diphenylpiperidine-3-carboxamide:

The ring's C=O carbon is shown by the chemical shift value of 204.6 ppm. The 2°amide's C=O carbon is shown by the chemical shift value at 170.2 ppm. The ipso carbons of phenyl rings are indicated by the peaks at 154.4–146.2 ppm (Majeed *et al.*, 2021). It is confirmed (Table 3) that the product has formed by these absorptions, which show that the molecule has three phenyl groups with distinct sites of attachment. The other phenyl ring carbons are present, as indicated by the signal at δ 131.1-107.8 (Salimova *et al.*, 2023). The chemical shift value of 64.6 ppm is attributed to the methine carbon at position C3 (He *et al.*, 2023). The chemical shift values at 51.8 and 38.3 ppm, respectively, correspond with the benzylic carbons at positions C2 and C6 (Sim *et al.*, 2022).

Antimicrobial Activity:

The antimicrobial activity was performed by the Disc diffusion technique method, using different concentrations (50 µg, 100 µg, 500 µg and 1000 µg). The sterile Muller hinton agar and Sabouraud dextrose agar were used for bacteria and fungi respectively (Dineshkumar and Parthiban, 2022). Two Gram positive, two Gram negative and two fungal strains were used to study the antimicrobial activity (Table 4, Fig. 1). All these strains were obtained from Pune (Kollman *et al.*, 2021). (NCIM-National Collection of Industrial Microbes) The Whatman Number 2 filter paper of 6 mm diameter was loaded with 100 µl of the diluted sample placed at equal intervals over the uniformly inoculated plate along with a standard disc Ciprofloxacin 5 mcg/disc for bacteria and Nystatin 100 units/disc for fungi were also placed along with sample to maintain quality control (Iliyasov *et al.*, 2022; Nguyen *et al.*, 2023; Bilgaiyan *et al.*, 2023; Borah *et al.*, 2023).

Solvent-DMSO:

Followed by incubation at 37ºC for 24 h and 25°C

Table 3: 13C NMR Spectral data of compound N-(3-chlorophenyl)-4-oxo-2,6-diphenylpiperidine-3-carboxamide

Chemical Shift (ppm)	Nature of the Peak	Assignment
204.6	1	C=O carbon of piperidinone ring
170.2	1	C=O carbon of 2° amide
154.4-146.2	3	Ipso carbons of phenyl rings
131.1-107.8	15	Other carbons of phenyl rings
64.6	1	Methine carbon at C_3
51.8-38.3	2	Benzylic carbons at C_2 and C_6
57.1	1	Methylene carbon at C_5

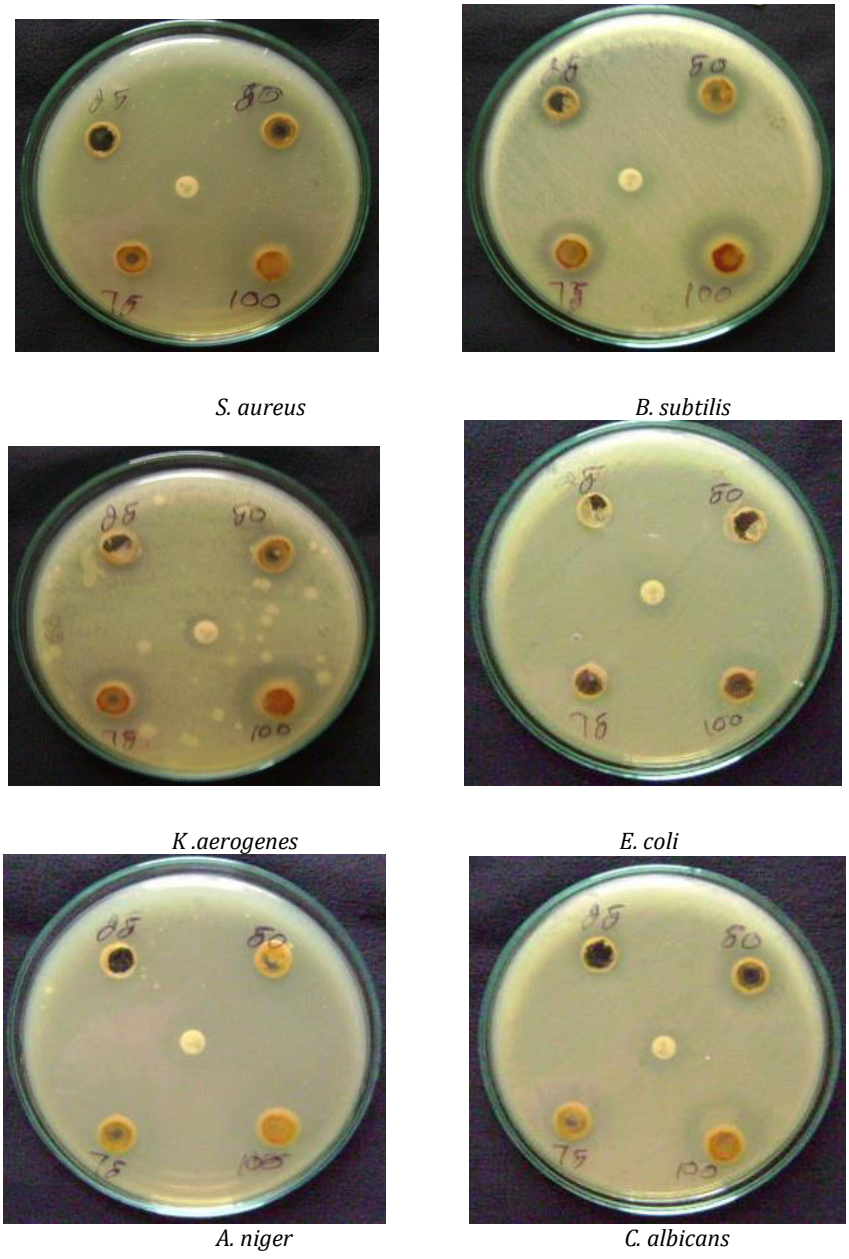

Fig. 1: Zone of Inhibition.

Table 4: Zone of inhibition in Antimicrobial activity

S. No.	Name of the Microorganisms	Zone of inhibition in mm					
		25 mcg	50 mcg	75 mcg	100 mcg	Solvent control	Standard
1	*Staphylococcus aureus* (NCIM2079)	15	15	18	19	-	35
2	*Basillus subtilis* (NCIM2063)	18	20	20	21	-	40
3	*Klebsiella aerogenes* (NCIM2098)	14	14	17	20	-	30
4	E.coli (NCIM2065)	15	15	16	18	-	38
5	*Aspergillus niger* (NCIM2105)	14	16	16	16	-	35
6	*Candida albicans* (NCIM3102)	13	15	15	18	-	32

Standard-Ciprofloxacin 5µg/disc for bacteria; Nystatin 100 units/disc for fungi.

for two days for bacteria and fungi were observed for zone of inhibition. The zone of inhibition was measured by using a standard scale (Vinokurov *et al*., 2023a). The diameter of the zone of inhibition was directly proportional to the amount of active constituent present in the sample (Pemawat *et al*., 2024). The compound were found to be effective against Gram positive (*Staphylococcus aureus* and *Basillus subtilis)* (Selvakumaran *et al*., 2023). Among these two Gram positive the effect was found to be remarkable at low concentration (100 mcg) towards *Basillus subtilis* and more effective against Gram negative *E. coli* and *Klebsiella aerogenes* (Buravlev and Shevchenko, 2023; Csuvik and Szatmári, 2023; Pu *et al*., 2023). The compound showed better response towards fungal strains *Aspergillus niger* and *Candida albicans* (Vinokurov *et al*., 2023b).

Conclusion

Mannich base contain compounds, particularly centered on those exhibiting antifungal properties. The reactions was carried out with equimolar amounts of the reactants in benzene at 60-70°C for 4–5 h, and the yields ranged from 68 to 80%. The synthesized compounds were characterized by physical constants, IR, ^{1}H and ^{13}C NMR, and mass spectra, and elemental analyses. Their antimicrobial activity was evaluated against gram-positive and gram-negative bacteria (*S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*). A results of antimicrobial screening made it possible to recommend the obtained Mannich bases for the design of new antimicrobial agents. Thus, as part of our interest in antifungal agents, this narrative review aimed to gather information from the literature on the synthesis of various representative Mannich–base-containing compounds, particularly centered on those exhibiting antibacterial, antifungal properties. The antibacterial and antifungal effect exhibited by Mannich bases of the heterocycles suggests that compounds that have a heterocyclic system attached to the β-amino core are attractive alternatives oriented to the synthesis of novel and helpful antibacterial and antifungal agents.

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