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MICROWAVE-ASSISTED SYNTHESIS AND ANTIMICROBIAL EVALUATION OF MANNICH BASE DERIVATIVES

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ABSTRACT

The significance of benzimidazole as a helpful scaffold in medicinal chemistry is highlighted by this study. An efficient method for creating novel bioactive compounds is demonstrated by the successful synthesis and characterisation of a novel Mannich base derivative. The molecule may be a promising option for future therapeutic development, particularly in addressing microbial resistance, according to the demonstrated antibacterial activity. Academically, this work advances our knowledge of the structure–activity connections in benzimidazole derivatives and offers a straightforward and trustworthy synthesis and analysis method. The precision of the structural confirmation is guaranteed by the employment of several characterisation techniques. The results provide practical support for the use of these compounds in the creation of novel antibacterial drugs.

Future research may concentrate on enhancing biological activity, examining mechanisms of action, and assessing safety profiles. All things considered, this study offers a helpful starting point for more research in synthetic chemistry and pharmacological applications.

Keywords: Benz imidazole; Benz Aldehyde, Urea, Mannich Base; Spectral Characterization; Antimicrobial Activity

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INTRODUCTION

The Mannich reaction which condenses an aldehyde, an amine and an active hydrogen-containing substrate to form β-amino carbonyl compounds (Mannich bases) is still one of the most flexible and commonly used carbon–carbon bond-forming reactions in organic chemistry. This reaction has several uses in synthetic, medical and pharmaceutical chemistry due to its ease of operation, benign reaction conditions and structural diversity of products.[1] Mannich base derivatives in particular have received a lot of attention because of their various processes in biology, which include anti-microbial, anti-cancer prevention, anti-inflammatory, and antioxidant properties.[2] Amino alkyl groups, which improve molecular solubility, bioavailability, and interaction with biological targets, are frequently blamed for these pharmacological effects. Since heterocyclic frameworks are present in a large percentage of clinically authorised medications, heterocyclic compounds are an essential class of bioactive chemicals. A possible method to improve biological activity and selectivity is the incorporation of heterocyclic moieties into a Mannich base derivative.[6] According to recent research, heterocyclic Mannich bases have a variety of medicinal properties, including antiviral, antineoplastic, anticonvulsant, and antipsychotic actions.[3] Despite these developments, a careful review of the literature identifies a significant research gap: many published studies mainly rely on synthetic approaches, with little attention paid to thorough physicochemical characterisation and connections between structure and property.[4] Moreover, systematic studies that combine morphological, crystallographic, and spectroscopic examinations to confirm structure and forecast functional performance are still lacking. This disparity becomes especially important in light of the expanding global problem of antimicrobial resistance (AMR), which calls for the creation of new substances with enhanced effectiveness and well-defined characteristics.[5-7] Sustainable

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Development Goal 3: Good Health and Well-Being, which highlights the need to fight infectious diseases and improve access to safe and effective therapeutic agents, is closely aligned with the current work in this respect. This work advances current efforts in drug discovery and the creation of next-generation antimicrobial medicines by creating and analysing novel Mannich base derivatives that may have biological significance.[8] Mannich bases have been shown to be useful in industrial and environmental applications, such as intermediates in the synthesis of agrochemicals, polymers and corrosion inhibitors, in addition to their pharmacological significance.[9-11] Additionally, their capacity to create stable complexes with transition metal ions has created new opportunities in coordination chemistry, where these complexes frequently display improved catalytic and biological characteristics.[12] However, the logical design and use of these compounds are limited by the lack of thorough structural validation in many investigations. Therefore, the primary objective of the current study is to conclude this identified research gap by developing a novel Mannich base derivative and performing comprehensive structural and physicochemical characterisation.[13-15] The produced compound was analysed using Fourier Transform Infrared spectroscopy, UV–visible spectroscopy, X-ray diffraction, and scanning electron microscopy to shed light on its functional groups, electronic transitions, crystallinity, and surface morphology. By establishing a clear structure–property link through this integrated analytical technique, the study aims to provide a strong scientific foundation for evaluating the compound's potential biological and pharmaceutical functions.

EXPERIMENTAL

Chemicals and Reagents

If otherwise indicated, every chemical utilised in this investigation was of analytical reagent (AR) grade and was employed without additional purification. Benzimidazole, urea, and formaldehyde were procured from SRL Chemicals Pvt Ltd, India. Ethanol and other solvents were of standard laboratory grade.

UV–Visible spectroscopy

It is an analytical technique for identifying how a substance absorbs light in the visible and ultraviolet regions of the electromagnetic spectrum

FT-IR analysis

Using KBr pellets and a Shimadzu FTIR-8300 spectrophotometer, infrared spectra were obtained in the 4000–400 cm^{-1} range.

SEM analysis

It is potent method for examining a material's surface morphology and microstructure at extremely high magnification and resolution.

XRD analysis

It is a fundamental technique to evaluate a material's crystalline structure, phase composition, and other structural features. It is especially important in the domains of materials science, nanotechnology, and medical research.

Melting Point Determination

A Mel-Temp device was used to determine the synthesised compound's melting point, which is reported uncorrected.

Thin Layer Chromatography

It is coated with silica gel was used to track the purity and reaction progress. Iodine vapour was used to visualise spots.

Synthesis of Mannich Base Derivative

Formaldehyde (2 mL, 0.1 M) and urea (0.1 M) were added after benzimidazole (0.1 M) was dissolved in ethanol. The reaction mixture was refluxed for six hours at 80°C after being stirred for thirty minutes at

room temperature.[16] The mixture was allowed to cool to room temperature after completion. Following filtration, the precipitate was vacuum-dried and washed with distilled water. The crude product from 100% ethanol was recrystallized to produce the pure Mannich base.

Reaction Consideration

Formaldehyde and urea combine in neutral to slightly alkaline environments to produce reactive intermediates such as methyl urea derivatives. The Mannich condensation is facilitated by the creation of various intermediates, which are controlled by pH, temperature, and reactant ratios.

Microbial Strains and Antimicrobial Activity

Staphylococcus aureus (MTCC 87) and *Candida albicans* (MTCC 183), which were collected from the Microbial Type Culture Collection and National Chemical Laboratory, were used to investigate the antibacterial activity. Mueller-Hinton agar (bacteria) and Sabouraud's dextrose agar (fungi) were subjected to the disc diffusion procedure.[24]

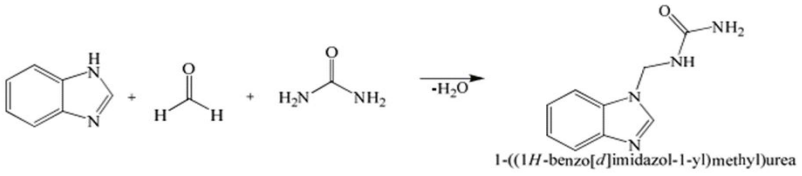
RESULTS AND DISCUSSION

Synthesis of Mannich Base

Benzimidazole, urea, and paraformaldehyde were combined in a 1:1:1 molar ratio to create the Mannich base derivative.[17] Thin-layer chromatography was used to monitor the reaction's progress and assess its completion after the reaction mixture was refluxed at 80°C for six hours. The product was separated, refined by recrystallization with 100% ethanol, and produced as a stable solid, demonstrating the effectiveness of the chosen synthesis pathway.

Physical characterization of the compound

Molecular formula	: $C_9H_{10}N_4O$
Molecular weight (g/ mol)	: 190.40
Melting Point (^{0}C)	: 175-180^{0}C



Scheme-1: Synthesis of Mannich Base

Ultraviolet Visible Spectral Analysis

The UV-visible spectra of the produced chemical revealed characteristic absorption bands in the 250–270 nm range, which matched the $\pi \rightarrow \pi^*$ transitions of the benzimidazole aromatic system. $n \rightarrow \pi^*$ transitions linked to lone pair electrons on nitrogen atoms found in both the urea moiety and the imidazole ring are responsible for a weaker absorption band seen in the 280–320 nm range (Fig.-1). These spectral features confirm the existence of a conjugated system by demonstrating electrical interactions between the urea group and the benzimidazole ring.[18] These interactions may affect the compound's chemical reactivity as well as its biological activity, since conjugated systems are often associated with enhanced antibacterial properties. The synthesised compound's purity and successful synthesis without notable impurities are shown by the existence of well-defined absorption bands. An extended delocalisation of electrons inside the aromatic system is suggested by the observed $\pi \rightarrow \pi^*$ transitions, which improves the molecule's overall stability. The suggested molecular structure is supported by the $n \rightarrow \pi^*$ transitions, which further verify the participation of heteroatoms (oxygen and nitrogen) in electronic interactions. If compared to normal compounds, the modest shift in absorption maxima could be a sign of intramolecular charge transfer interactions and substituent effects.

Fourier Transform Infrared Spectroscopy

The synthesised compound included significant functional groups. The emergence of the strong C=O stretching band about 1630–1690 cm^{-1} and the N–H stretching vibrations of the urea group in the 3300–

3500 cm^{-1} area proved the urea functionality (Fig.-2). Aromatic C–H stretching vibrations of the benzimidazole ring were found in the 3000–3100 cm^{-1} range, whereas characteristic C=C stretching bands appeared between 1400 and 1600 cm^{-1}.

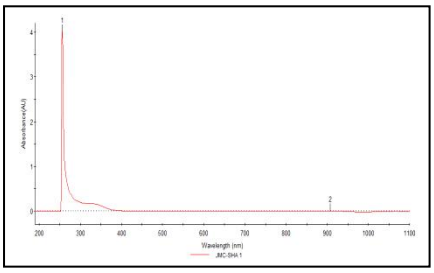


Fig.-1: UV- Visible Spectra of Mannich Base Derivative

Moreover, C–N stretching vibrations in the 1200–1350 cm^{-1} range assist the formation of the imidazole structure. These results collectively show that the urea and benzimidazole moieties were successfully combined to create the Mannich base.[19] Because urea-containing compounds frequently exhibit intermolecular hydrogen bonding, the observed N–H stretching vibrations may exhibit a small widening. The urea functional group's structural stability and potential involvement in hydrogen bonding interactions are confirmed by the strong C=O stretching band. The creation of the Mannich base connection is further confirmed by the distinctive C–N stretching vibrations, indicating effective condensation.

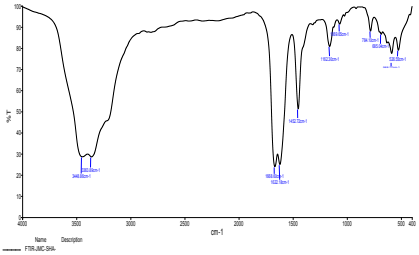


Fig.-2: FTIR Spectra of Mannich Base Derivative

Scanning Electron Microscopy

The resulting chemical's surface shape and particle dispersion. The fairly uniform particle distribution and somewhat defined surface feature of the micrographs demonstrated the good homogeneity of the synthetic material. Controlled nucleation and development during synthesis are indicated by the observed morphology. Because it can affect dissolution rate, bioavailability, and overall biological performance, such consistency is beneficial for pharmaceutical applications. Intermolecular interactions during the drying process could be the cause of the slight aggregation seen in some areas. The observed surface shape suggests stable particle production, which may result in improved physicochemical properties.[20] The slight aggregation observed may be the result of hydrogen bonding interactions or van der Waals forces between particles (Fig.-3).

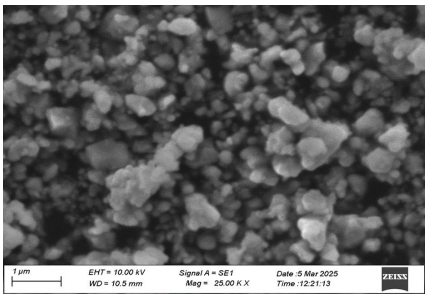


Fig.-3: SEM Analysis of Mannich Base Derivative

X-Ray Diffraction Studies

The synthetic material was crystalline. The diffraction pattern's clear, crisp peaks at specific 2θ values demonstrated high crystallinity and phase purity. Discrete peaks indicate an ordered crystal lattice, and the absence of significant amorphous halos confirms low structural disorder (Fig.-4). The calculated d-spacing values (based on Bragg's law) and the observed diffraction peaks, which correlate to specific crystal planes, provide additional evidence for the formation of a discrete crystalline structure. High crystallinity is often associated with improved stability, which is beneficial for storage and potential medical applications.[21] Micro strain inside the lattice and small crystallite size could be the cause of any little peak broadening seen in the diffraction pattern. The successful development of the expected structure is further confirmed by the agreement of peak positions with standard diffraction patterns (if compared). Improved mechanical strength and thermal stability are crucial for handling and storing pharmaceuticals, and high crystallinity may help. [22] Drug dissolving behaviour can also be influenced by the crystalline nature; an ideal ratio of crystallinity to amorphous content is frequently preferred. Intermolecular interactions and overall stability may be impacted by the ordered structure's potential to improve molecular packing efficiency.

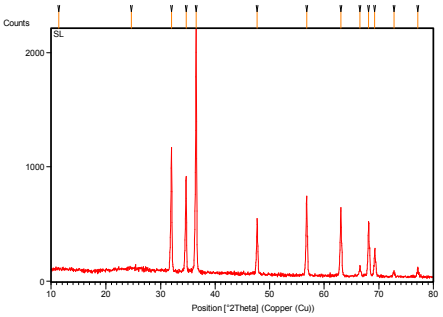


Fig.-4: XRD Analysis of Mannich Base Derivative

Sustainable Development Goal (SDG) Relevance

By advancing the creation of innovative antimicrobial agents, this research supports Sustainable Development Goal 3. The search for novel compounds with enhanced efficacy is necessary due to the growing resistance of infections to current medications. The synthesised Mannich base shows promise as an antibacterial candidate, boosting international efforts to fight infectious diseases.

Antimicrobial Activity of the Sample

At 100 µg/mL, the sample exhibited strong antibacterial activity against *Staphylococcus aureus* with a maximum zone of inhibition of 10 mm.[23-24]

At the same concentration, it also showed (Table-1) notable antifungal activity against *Candida albicans* with a zone of inhibition of 5 mm (Fig.-5).

Table-1: Antimicrobial Activity of Sample

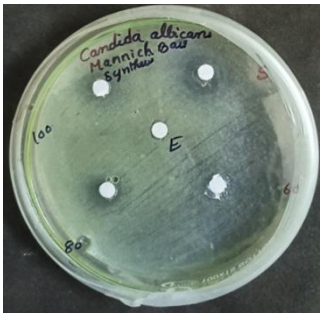
Samples	Concentrations (µg/ml)	Organisms/Zone of inhibition (mm)	
		Staphylococcus aureus	*Candida albicans*
Samples	60	6	1
	80	8	3
	100	10	5
Amoxicillin	10 µl/disc	8	-
Fluconazole	10 µl/disc	-	13
Ethanol	10 µl/disc	-	-

CONCLUSION

In this study, the Mannich base derivative was effectively synthesised by a straightforward and efficient technique. FT-IR, UV-visible spectroscopy, XRD, and SEM structural characterisation verified the compound's production, functional integrity, and crystalline nature. The synthetic derivative's promise as

a bioactive chemical was demonstrated by its significant antimicrobial activity against specific bacterial and fungal strains.

Staphylococcus Aureus



Candida albicans

Fig.-5: Antimicrobial Samples

These results emphasise the significance of Mannich bases based on benzimidazoles as viable options for the creation of novel antibacterial drugs. However, more research is advised to determine its suitability for pharmaceutical applications, including thorough toxicity studies, mechanism of action, and evaluation against a wider range of pathogens. By encouraging the continuous search for new chemicals to fight microbial resistance and enhance global health outcomes, our effort supports Sustainable Development Goal-3.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

The present work is aligned with *SDG-3: Good Health and Well-Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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