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MICROWAVE ASSISTED SYNTHESIS OF BENZOTRIAZOLE DERIVATIVES AS POTENTIAL TO ANTI-MICROBIAL AGENTS

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ABSTRACT

The current research shows a rapid, clean, and environmentally sustainable method of the microwave-assisted synthesis of benzotriazole derivatives. The use of microwave irradiation significantly enhanced reaction efficiency, offering a rapid, energy-efficient, and environmentally friendly alternative to conventional synthetic methods. Microwave conditions led to improved yields and reduced reaction times, demonstrating the advantages of green chemistry in heterocyclic synthesis. The synthesized benzotriazole derivatives were characterized using **Fourier Transform Infrared Spectroscopy (FTIR)**, which confirmed the presence of characteristic functional groups such as N–H, C=N, and aromatic C–H stretches, validating the successful formation of the target compounds. Additionally, **Thin Layer Chromatography (TLC)** was employed to monitor the progress of the reactions and confirm the purity of the synthesized products, where distinct Rf values helped in differentiating between intermediates and final products.The **antimicrobial screening** of the synthesized compounds revealed promising results, with several derivatives showing significant activity against both Gram-positive and Gram-negative bacterial strains, as well as selected fungal pathogens. These findings support the hypothesis that structural modification of the benzotriazole nucleus can enhance biological activity and provide new leads for antimicrobial drug development. In conclusion, this study not only demonstrates the effectiveness of **microwave-assisted synthesis** for preparing benzotriazole derivatives, but also highlights the **potential of these compounds as antimicrobial agents**. The integration of analytical methods like **FTIR** and **TLC** further ensured the reliability and reproducibility of the synthesis process.

KEYWORDS: Microwave assisted synthesis, Benzotriazole derivatives, anti-microbial agents.

INTRODUCTION

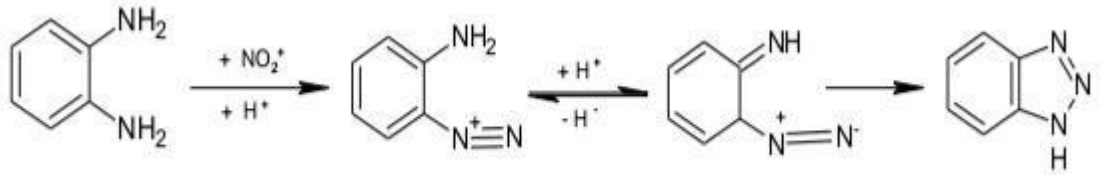
Microwave-assisted synthesis is a branch of green chemistry. Microwave-assisted synthesis has gained much attention in recent years. Microwave irradiation-assisted chemical transformations are pollution free, eco-friendly and offer high yields together with simplicity in processing and handling. Because of the increasing bacterial resistance to antibiotics, the discovery and development of novel antimicrobials is one of the most important fields of research today. Derivatization of heterocyclic pharmacophores represents a versatile approach to generate chemical diversity for lead identification and optimization. Benzotriazoles have found wide applications in organic synthesis, as dyestuffs and fluorescent compounds, corrosion inhibitors, photo stabilizers and agrochemicals.[1] Benzotriazole is a good leaving group and it has been widely used as synthetic auxiliary in organic synthesis.[2] The synthesis of furthermore functionalized benzotriazoles is considered to become important subjects of synthetic and biological researches since they are expected to exhibit novel properties applicable to such fields. On the other hand, benzotriazole derivatives have shown potential antimycobacterial[4], antitubercular[5], antitumor[6], antiproliferative[7,8], anesthetic[9], and anti-inflammatory activities.[10,11] Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions.[12-16] Microwave reactions under solvent-free conditions are attractive in offering reduced pollution and offer low cost together with simplicity in processing and handling.[17-20] Nalkylation of aromatic compounds involving nitrogen heterocycles are important reactions in organic synthesis. Our previous report on the synthesis and antimicrobial activities of N-alkylated benzotriazole unraveled that N-substituted groups attributed their role in enhancing the activity.[21] Inspired by these results, in the present investigation we designed and synthesized a novel benzotriazole derivatives having heteroaromatic moieties.

A green chemistry approach for organic synthesis is describe here, which involves microwave exposure of reactants in presence or absence of solvents. A novel and simple method will be developed for the synthesis of some benzotriazole derivatives under microwave irradiation.The synthesized compounds have been characterized and confirmed by TLC, elemental analysis, FTIR spectroscopy and screened for their antibacterial activity.

SCHEME

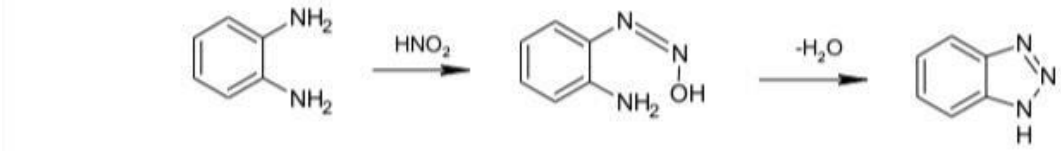
Scheme-I for synthesis of benzotriazole

- Benzotriazoles are synthesized by cyclocondensation of o-phenylenediamines with sodium nitrite in acetic acid. The Reaction involved the simple heating the reagents together. Conversion of the diamine into the monodiazonium Derivative is followed by spontaneous cyclization.



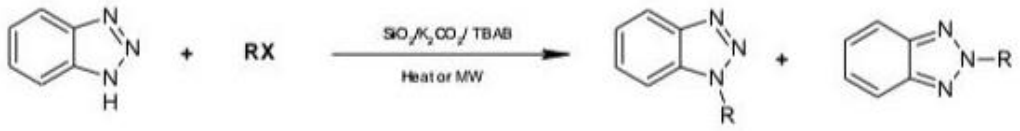
Scheme-II

- 1,2,3-Benzotriazole has been prepared directly by the action of nitrous acid on o-phenylenediamine and by the hydrolysis of an acylated or aroylated benzotriazole which has been previously prepared by the action of nitrous acid on the corresponding mono acylated or aroylated o-phenylenediamine. The above procedure is the direct method and gives better over-all yields than the methods involving several intermediate steps.



Scheme-III N-Alkylation of Benzotriazole under Solvent-Free Conditions.

- N-Alkylation of Benzotriazole under Solvent-Free Conditions: An efficient, simple and solvent-free method for highly regioselective N-alkylation of benzotriazole in the presence of SiO2, K2CO3 and tetrabutylammonium bromide (TBAB) under thermal and microwave conditions has been described. In this method, 1-alkyl benzotriazoles were obtained regioselectively in moderate to high yields and short reaction times.[15]



R= Alkyl, Aryl

METHODOLOGY

Synthesized Benzotriazole derivatives

In a dry 50 mL round-bottom flask (RBF), 1 mmol of benzotriazole was introduced. To this, a heterogeneous mixture consisting of silicon dioxide (SiO_2, 500 mg), potassium carbonate (K_2CO_3, 2 mmol), and tetrabutylammonium bromide (TBAB, 0.1 mmol) was added. This combination served multiple roles: silicon dioxide acted as a solid support to enhance surface contact, potassium carbonate as a mild base to facilitate deprotonation of the benzotriazole, and TBAB as a phase transfer catalyst to increase the reactivity under solvent-free or minimal solvent conditions. Following this, a catalytic amount of dimethylformamide (DMF, ~0.5 mL) was added to assist in mixing the reagents thoroughly and to mildly solubilize the organic components.

Subsequently, 1.2 mmol of acetic anhydride was added dropwise to the reaction mixture while stirring. The flask was then placed inside a microwave reactor and irradiated at 180 W for 4 minutes and 20 seconds. The reaction progress was visually monitored, and the short irradiation time ensured minimal decomposition and efficient energy input.

Upon completion of the microwave irradiation, the hot reaction mixture was immediately poured into a beaker containing ice-cold distilled water (20–30 mL). This caused the desired N-acetylbenzotriazole to precipitate

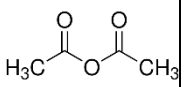
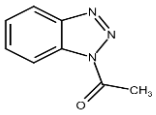
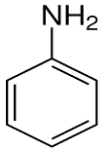
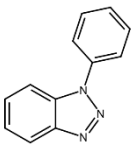
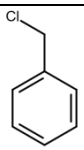
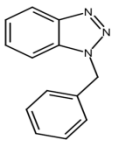
out of the aqueous phase as a white solid. The crude product was collected by vacuum filtration, washed thoroughly with cold water to remove inorganic residues and excess reagents, and then air-dried or placed in a desiccator. The resulting solid was obtained in high purity and could be recrystallized from ethanol if further purification was required. The identity and purity of the product could be confirmed via TLC, melting point analysis, and spectroscopic methods.

N-Acetyl benzotriazole is a white to off-white crystalline solid with a reported melting point of 78°C. It is sparingly soluble in water, which allows for its easy isolation by precipitation when the reaction mixture is poured into ice-cold water. The compound is readily soluble in common organic solvents such as ethanol, methanol, dimethyl sulfoxide (DMSO).

N-Phenyl benzotriazole, also known as 1-Phenyl-1H-benzotriazole is an aromatic heterocyclic compound with the molecular formula **$C_{12}H_9N_3$**. It appears as a white to pale yellow crystalline solid. The compound exhibits a melting point in the range of 103°C. N-Phenylbenzotriazole is practically insoluble in water but dissolves readily in a variety of organic solvents including ethanol, methanol, acetone, benzene, chloroform, and DMSO.

1-Benzyl-1H-benzotriazole is an organic compound with the molecular formula $C_{13}H_{11}N_3$. It is a white to off-white crystalline solid under standard conditions. The compound has a melting point ranging from 118 **°C**. In terms of solubility, it is readily soluble in most organic solvents such as ethanol, methanol, acetone, chloroform, and dimethyl sulfoxide (DMSO), making it suitable for a variety of organic reactions and applications.

SYNTHESIZED COMPOUNDS

S.No	Compound name	Structure of reactant	Product	% yield	Melting point	Solubility	MicrowaveTime taken
1.	N-acetyl benzotriazole	 Acetic anhydride		81.3%	47°C	Readily soluble in polar solvents	4 min 26 sec
2.	N-phenyl benzotriazole	 aniline		75%	103°C	Soluble in organic solvents.	4 min 38 sec
3.	1-Benzyl-1H-benzotriazole	 Benzyl chloride		85.8%	118°C	moderately soluble in polar solvents	5 min 8 sec

CHEMICAL EVALUATION

A. Determination of Rf value by thin layer chromatography

Thin layer chromatography uses a thin glass plate coated with either aluminum oxide or silica gel as the solid phase. The mobile phase is a solvent chosen according to the properties of the components in the mixture. The principle of TLC is the distribution of a compound between a solid fixed phase (the thin layer) applied to a glass or plastic plate and a liquid mobile phase (eluting solvent) that is moving over the solid phase. A small amount of a compound or mixture is applied to a starting point just above the bottom of TLC plate.

The plate is then developed in the developing chamber that has a shallow pool of solvent just below the level at which the sample was applied. The solvent is drawn up through the particles on the plate through the capillary action, and as the solvent moves over the mixture each compound will either remain with the solid phase or dissolve in the solvent and move up the plate. Whether the compound moves up the plate or stays behind depend on the physical properties of that individual compound and thus depend on its molecular structure, especially functional groups.

When the solvent front has moved to within about 1 cm of the top end of the adsorbent (after 15 to 45 minutes), the plate should be removed from the developing chamber, the position of the solvent front marked, and the solvent allowed to evaporate. If the components of the sample are colored, they can be observed directly. If not, they can sometimes be visualized by shining ultraviolet light on the plate or by allowing the plate to stand for a few minutes in a closed container in which the atmosphere is saturated with iodine vapor. Sometimes the spots can be visualized by spraying the

plate with a reagent that will react with one or more of the components of the sample.

The components, visible as separated spots, are identified by comparing the distances they have traveled with those of the known reference materials. Measure the distance of the start line to the solvent front. Then measure the distance of center of the spot to the start line. Divide the distance the solvent moved by the distance the individual spot moved. The resulting ratio is called Rf-value. As the chemicals being separated may be colorless, several methods exist to visualize the spots. Often a small amount of a fluorescent compound, usually manganese activated zinc silicate, is added to the adsorbent that allows the visualization of spots under a blacklight (UV254). The adsorbent layer will thus fluoresce light green by itself, but spots of analyte quench this fluorescence, Iodine vapors are a general unspecific color reagent, Specific color reagents exist into which the TLC plate is dipped or which are sprayed onto the plate. Once visible, the Rf value, or retention factor, of each spot can be determined by dividing the distance traveled by the product by the total distance traveled by the solvent (the solvent front). These values depend on the solvent used, and the type of TLC plate, and are not physical constants.

The behavior of an individual compound in TLC is characterized by a quantity Known as R*f* and is expressed as a decimal fraction. The R*f* is calculated by dividing the distance the compound traveled from the original position by the distance the solvent travelled from the original position (the solvent front).

PROCEDURE

Dissolve a small quantity (~1-2 mg) of benzotriazole derivatives in an appropriate solvent (e.g., methanol or dichloromethane) to prepare a dilute solution suitable for spotting.

Use a clean, dry silica gel TLC plate. With a pencil, draw a straight baseline about 1 cm from the bottom edge of the plate.

Mark small spots along the baseline where the sample will be applied (usually 1 or 2 spots). Using a capillary tube or micropipette, apply a small drop of the product solution onto the marked spots.

Allow the spots to dry; if necessary, apply the sample multiple times carefully to get a concentrated but non-diffused spot.

Select an appropriate solvent system for the compounds : Ethyl acetate: Hexane (7:1)

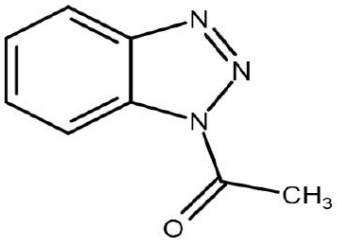
Pour a small amount (~10-15 mL) of the solvent system into the developing chamber. Close the chamber and allow it to equilibrate for 15–20 minutes.

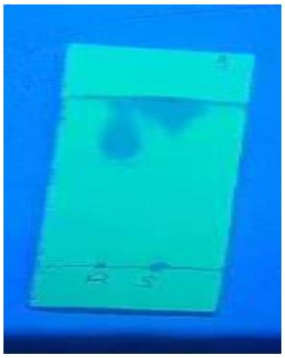
Carefully place the spotted TLC plate vertically inside the chamber, ensuring the baseline is above the solvent level. Close the chamber and allow the solvent front to travel up the plate until it is about 1-2 cm from the top edge (this usually takes 10-20 minutes). Remove the plate from the chamber. Mark the solvent front immediately with a pencil. Allow the plate to dry completely.

Examine the plate under UV light (254 nm or 365 nm), as compounds often absorbs UV light. Mark the position of the compound spot with a pencil.

Rf value of N-acetylbenzotriazole

Rf = (Distance traveled by the compound) / (Distance traveled by the solvent front)



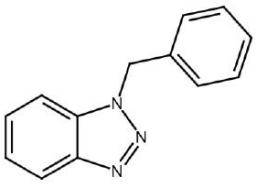


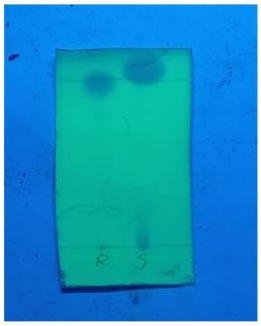
Rf = (Distance traveled by the compound) / (Distance traveled by the solvent front)

Benzotriazole=2.5cm , Solvent=4cm Sample=3.0cm, Solvent=4cm

Rf =2.5/4 =0.625 Rf=3/4 =0.75

Rf value of 1-Benzyl-1H-benzotriazole



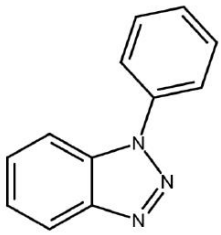


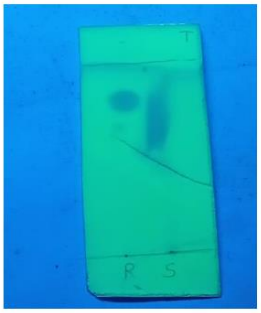
Rf = (Distance traveled by the compound) / (Distance traveled by the solvent front)

Benzotriazole=3.2cm , Solvent=3.5cm Sample=3.3cm, Solvent=3.5cm

Rf=3.2/3.5 =0.91 Rf=3.3/3.5 =0.94

Rf value of N-phenylbenzotriazole





Rf = (Distance traveled by the compound) / (Distance traveled by the solvent front)

Benzotriazole=3.3cm , Solvent=4cm Sample=2.2cm, Solvent=4cm

Rf=3.3/4 =0.825 Rf=2.2/4 =0.55

B. Fourier transform Infrared Spectroscopy Analysis

- In FTIR analyses, Infrared light from the light source passes through a Michelson interferometer along the optical path. The Michelson interferometer comprises a beam splitter, moving mirror, and fixed mirror. The light beam split into two by the beam splitter is reflected from the moving mirror and fixed mirror, before being recombined by the beam splitter.
- As the moving mirror makes reciprocating movements, the optical path difference to the fixed mirror changes, such that the phase difference changes with time. The light beams are recombined in the Michelson interferometer to produce interference light. The intensity of the interference light is recorded in an interferogram, with the optical path difference recorded along the horizontal axis.
- Fourier transform infrared spectroscopy (FTIR) is a technique which is used to obtain infrared spectrum of absorption, emission, and photoconductivity of solid, liquid, and gas.
- It is used to detect different functional groups in Compound. FTIR spectrum is recorded between 4000 and 400 cm^{-1}.
- **KBr Disc Technique:** Solid samples that are difficult to melt or dissolve in any acceptable IR transmitting liquids are employed as pellets. Around 100 mg of dry potassium bromide (or other alkali halide) powder is thoroughly mixed with the sample (0.5 to 1.0 mg), which is then crushed to a fine powder. The mixture is squeezed into a clear disc by using enough pressure. The band distortion brought on by radiation scattering will be reduced if the sample particles are grounded to 2 m or less in size. Due to absorbed moisture, the IR spectra created by the pellet approach frequently show bands at 3450 cm-1 and 1640 cm-1

N-acetyl benzotriazole

IR (KBr): ν_{max}3024.47 (Aromatic str. -CH), 2808.53 (Aliphatic str. -CH), 1516.66 (C-N str.), 1422.28 (N=N str.), 744.29 (-CH bend) cm^{-1}.

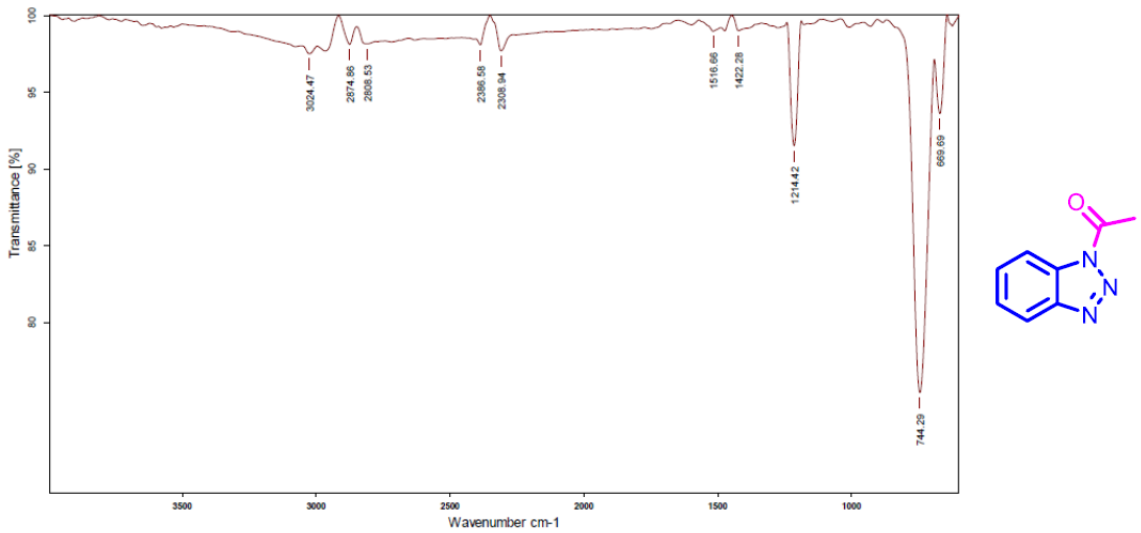


Figure 1: FTIR spectrum of N-acetyl benzotriazole.

- The structures of the synthesized compounds were confirmed using FTIR.
- The FTIR spectrum (KBr pellet) exhibits characteristic absorption bands confirming the functional groups present in the compound.
- The strong absorption at 3024.47 cm^{-1} corresponds to the aromatic C–H stretching vibrations, indicating the presence of aromatic rings.
- A peak at 2808.53 cm^{-1} is attributed to aliphatic C–H stretching, suggesting alkyl substituents.
- The band observed at 1516.66 cm^{-1} is assigned to C–N stretching, consistent with the presence of amine or related nitrogen-containing groups.
- The absorption at 1422.28 cm^{-1} is indicative of the N=N stretching vibration, characteristic of azo linkages. Finally, the band at 744.29 cm^{-1} corresponds to the bending vibrations of the –CH groups, supporting the structural features inferred from the higher frequency bands.

1-Benzyl-1H-Benzotriazole

IR (KBr): ν max 2961.76 (Aromatic str. -CH), 2877.96 (Aliphatic str. -CH), 1381.45 (C-N str.), 1476.68 (N=N str.), 745.39 (-CH bend) cm -1.

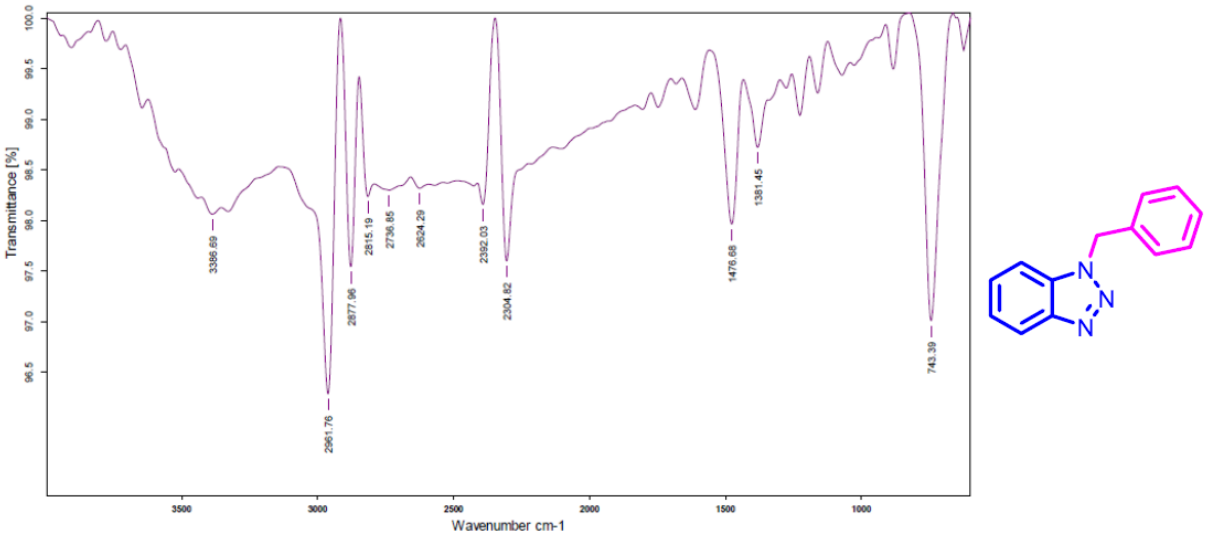


Figure 2: FTIR spectrum of 1-Benzyl-1H-Benzotriazole.

- The structures of the synthesized compounds were confirmed using FTIR.
- The FTIR spectrum (KBr pellet) shows key absorption bands that reveal important structural features of the compound.

- The peak at 2961.76 cm^{-1} corresponds to aromatic C–H stretching vibrations, confirming the presence of aromatic rings.
- The absorption at 2877.96 cm^{-1} is assigned to aliphatic C–H stretching, indicating alkyl groups in the molecule.
- The band at 1381.45 cm^{-1} is characteristic of C–N stretching, suggesting nitrogen-containing functionalities.
- The absorption near 1476.68 cm^{-1} corresponds to the N=N stretching vibration, indicative of azo or diazo linkages. Lastly, the peak at 745.39 cm^{-1} is attributed to the bending vibrations of the –CH groups, consistent with the substitution pattern on the aromatic ring.

N-Phenylbenzotriazole

IR (KBr): ν_{max}2880.39 (Aromatic str. -CH), 2817.42 (Aliphatic str. -CH), 1555.69 (C-N str.), 1404.61 (N=N str.), 752.53 (-CH bend) cm^{-1}.

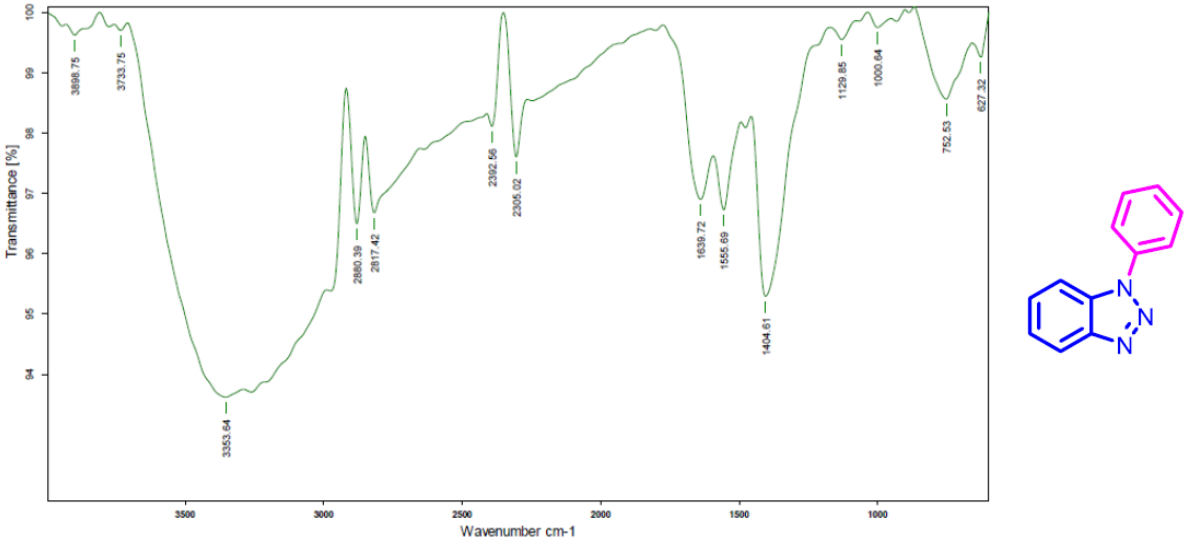


Figure 3: FTIR spectrum of N-Phenylbenzotriazole.

- The structures of the synthesized compounds were confirmed using FTIR.
- The FTIR spectrum (KBr pellet) displays characteristic absorption peaks indicative of the compound's functional groups.
- The band at 2880.39 cm^{-1} corresponds to aromatic C–H stretching vibrations, confirming the presence of aromatic rings.
- The absorption at 2817.42 cm^{-1} is due to aliphatic C–H stretching, suggesting the presence of alkyl substituents.
- A strong peak at 1555.69 cm^{-1} is attributed to C–N stretching, indicating nitrogen-containing groups within the structure.
- The band observed at 1404.61 cm^{-1} is assigned to N=N stretching vibrations, characteristic of azo linkages. Finally, the absorption at 752.53 cm^{-1} corresponds to the bending vibrations of –CH groups, supporting the aromatic substitution pattern.

PHARMACOLOGICAL EVALUATION

Antimicrobial Activity

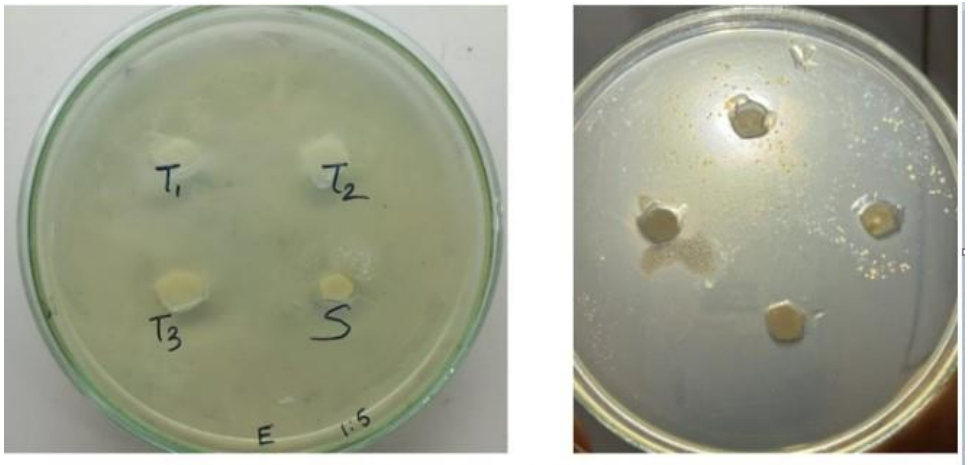
All synthesized compounds were screened for in vitro antibacterial activity against one-gram positive strain of bacteria (S. *aureus*) and one-gram negative strain of bacteria (E. *coli*) by cup plate method and Cefodoxamine was taken as standard.

Cup Plate Method

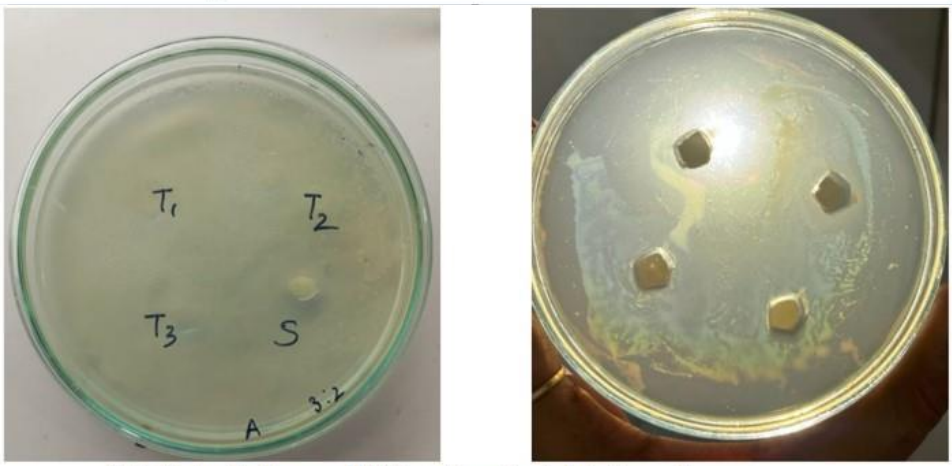
The nutrient agar medium was prepared by dissolving commercially available agar in distilled water.

- Immediately it was then autoclaved and cooled to 45 - 50 °C. The nutrient agar medium was inoculated aseptically with 0.5ml of strains of S. *aureus* and E. *coli* at room temperature.
- Into each sterile Petri dish about 15ml of inoculated molten agar medium was poured. The plates were left at room temperature for solidification. After solidification, the cups of 6mm diameter Petri dish and were made by scooping out the medium with the sterilized corn borer from Petri dish and were labeled.
- All the synthesized compounds and standard (cefodoxamine) were dissolved in DMSO to prepare appropriate dilution to get required concentration of 25µg/ml, 50µg/ml and 100µg/ml.
- The solutions of each compound, standard (cefodoxamine) and a control (DMSO) were added separately into each cup. The plates were kept undisturbed for about 24 hours at room temperature.

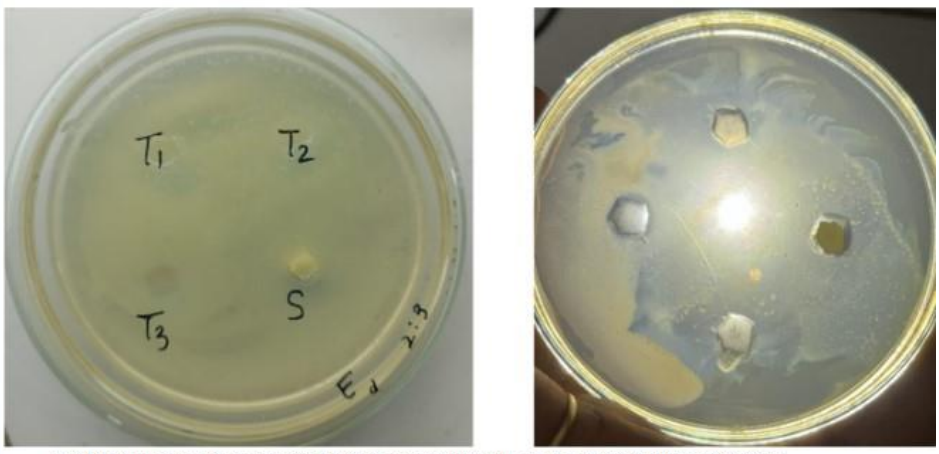
- After incubation period of 24 hours the diameter of zone of inhibition was measured with the help of antibiotic zone reader.



Petri dish showing the zone of inhibition of Benzotriazole derivatives on *E.coli.*



Petri dish showing the zone of inhibition of benzotriazole derivatives on *S.aureu.*



Petri dish showing the zone of inhibition of benzotriazole on *E.coli* with different dilutions.

Figure 4: Antibacterial activity of compounds against S. *aureus* (gram positive bacteria).

Table 1: Antibacterial activity of compounds against S. aureus (gram positive bacteria).
Zone of inhibition.

Concentration	20 mg/ml	40 mg/ml	60 mg/ml
T1	14 mm	10 mm	19 mm
T2	12 mm	14 mm	14 mm
T3	11 mm	16 mm	20 mm

Standard	16 mm	19 mm	23 mm

Table 2: Antibacterial activity of compounds against E. coli (gram negative bacteria). Zone of inhibition.

Concentration	20 mg/ml	40 mg/ml	60 mg/ml
T1	8 mm	12 mm	15 mm
T2	7 mm	10 mm	20 mm
T3	10 mm	15 mm	16 mm
Standard	16 mm	19 mm	23 mm

CONCLUSION

- In summary, the current research shows a rapid, clean, and environmentally sustainable method of the microwave-assisted synthesis of benzotriazole derivatives.
- The use of microwave irradiation significantly enhanced reaction efficiency, offering a rapid, energy-efficient, and environmentally friendly alternative to conventional synthetic methods. Microwave conditions led to improved yields and reduced reaction times, demonstrating the advantages of green chemistry in heterocyclic synthesis.
- The synthesized benzotriazole derivatives were characterized using **Fourier Transform Infrared Spectroscopy (FTIR)**, which confirmed the presence of characteristic functional groups such as N–H, C=N, and aromatic C–H stretches, validating the successful formation of the target compounds. Additionally, **Thin Layer Chromatography (TLC)** was employed to monitor the progress of the reactions and confirm the purity of the synthesized products, where distinct Rf values helped in differentiating between intermediates and final products.
- The antimicrobial screening of the synthesized compounds revealed promising results, with several derivatives showing significant activity against both Gram-positive and Gram-negative bacterial strains, as well as selected fungal pathogens. These findings support the hypothesis that structural modification of the benzotriazole nucleus can enhance biological activity and provide new leads for antimicrobial drug development.
- In conclusion, this study not only demonstrates the effectiveness of microwave-assisted synthesis for preparing benzotriazole derivatives, but also highlights the potential of these compounds as antimicrobial agents. The integration of analytical methods like FTIR and TLC further ensured the reliability and reproducibility of the synthesis process.

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