World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

SYNTHESIS, CHARACTERIZATION AND ANTI-BACTERIAL ACTIVITY OF NOVEL 1, 2, 4-TRIAZOLE DERIVATIVES

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Article Received on 05/06/2025 **Article Revised on 26/06/2025** **Article Accepted on 16/07/2025**

ABSTRACT
Modified 1, 2, 4-triazole nucleus have made a tremendous significance in medicinal chemistry. 1, 2, 4-triazoles and their derivatives are found to have wide variety of pharmacological uses such as anti-fungal, anti-viral , anti-bacterial, anti-inflammatory, anti-tumour, anti-oxidant, anti-tuberculosis etc. In this study we have synthesized some bioactive triazole derivatives and found to have a good anti-bacterial property. In this, we have studied on 4-chlorobenaldehyde and Furfuryldehyde substituted triazole derivatives.

KEYWORDS: 1, 2, 4-triazole, anti-bacterial activity, 4-chlorobenzaldehyde, Furfuryldehyde substituted triazole.

1. INTRODUCTION

Triazoles are heterocyclic compounds containing three nitrogen (N) atoms and two double bonds that have five members. Due to their importance in synthesis and biology, 1, 2, 4-triazole chemistry and its fused heterocyclic derivatives have garnered a lot of attention in recent decades. The 1,2,3-trizole moiety has been identified in a number of therapeutically interesting drug candidates, including antifungal, antibacterial, analgesic, anti-inflammatory, antineoplastic, antiviral, anticonvulsant, anxiolytic, antihistaminic, and CNS stimulants, among others.[1-8]

Life-threatening systemic bacterial and fungal infections have grown more prevalent in immune compromised hosts. The InhA inhibitory action of triazole derivatives is being investigated more and more. Isoniazid typically inhibits InhA, an important enzyme in the FASH system that is involved in the formation of mycobacterial mycolic acids. The possible antiviral and anti-tumoral properties of 1, 2, 4-triazole in general are being investigated. Examples of these substances with 1, 2, 4-triazole residues include the strong antiviral N-nucleoside ribavirin and the azole antifungal fluconazole.[9]

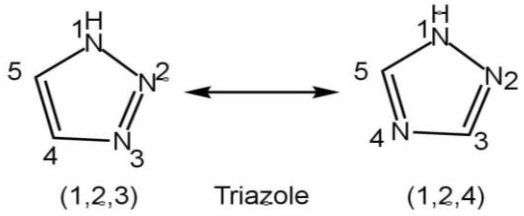


Fig.1.

2. MATERIALS AND METHODS

For the synthesis of 1, 2, 4-triazole derivatives, the required reagents, starting materials and solvents were purchased from a lab chemical supplier. The melting points of the synthesized compounds were determined by melting point apparatus. Other characteristics like TLC & Solubility of these synthesized compound were determined.

Further structural characterization studies were done by using IR and 1H-NMR.

2.1 REQUIRED CHEMICALS

Table 1.

S.NO	NAME OF CHEMICALS	S.NO	NAME OF CHEMICALS
1	Isoniazid	8	Benzaldehyde
2	Potassium thiocyanate	9	4-methoxy benzaldehyde
3	Mono chloro acetic acid	10	Furfuryldehyde
4	Anhydrous sodium acetate	11	4-chloro benzaldehyde

5	Dimethyl formamide	12	Formaldehyde
6	Glacial acetic acid	13	Hydrochloric acid
7	Acetic anhydride	14	Potassium hydroxide
		15	Ethanol

2.2 GENERAL PROCEDURE FOR SYNTHESIS OF SUBSTITUTED 1, 2, 4-TRIAZOLE

- **Synthesis of substituted Mercapto triazoles**

INH (0.1 mol) was dissolved inn 10% hydrochloric acid (100 ml) and Potassium thiocyanate (0.2 mol) was added on it. The resultant mixture was heated on a water bath for 5 hours. The obtained mixture was cooled, obtained solid was filtered and re-crystallized from ethanol to obtain the aryl thiosemicarbazide (88%). A mixture of this aroyl thiosemicarbazide (0.1 mol) and aqueous 5% potassium hydroxide solution (100 ml) was refluxed for 3 hours. The reaction mixture was poured into crushed ice and acidified with dilute hydrochloric acid. The precipitate thus obtained was filtered, dried and recrystallized from ethanol.[13]

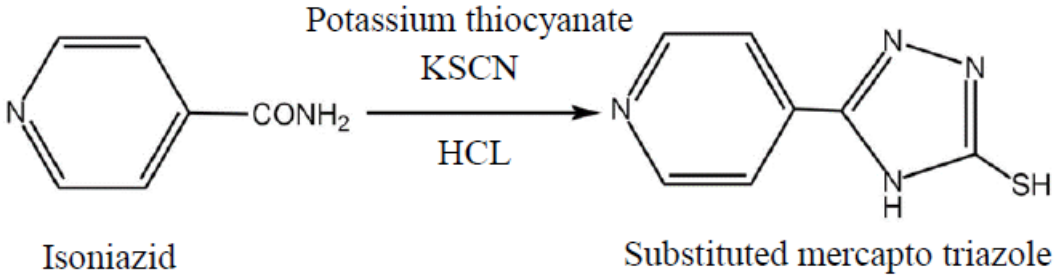


Fig.2.

- **Synthesis of substituted 1, 2, 4-Triazole from mercapto triazoles.**

A mixture of the mercaptotriazole (0.01 mol), monochloroacetic acid (0.015 mol), anhydrous sodium acetate (0.024 mol), glacial acetic acid (20 ml), acetic anhydride (15 ml) and substituted benzaldehyde (0.01 mol) was heated to reflux for 6-8 h. The reaction mixture was cooled and poured into crushed ice with vigorous stirring. The solid precipitate was filtered, washed with lukewarm water, dried and recrystallized from ethanol and dimethyl formamide (1:1).[13]

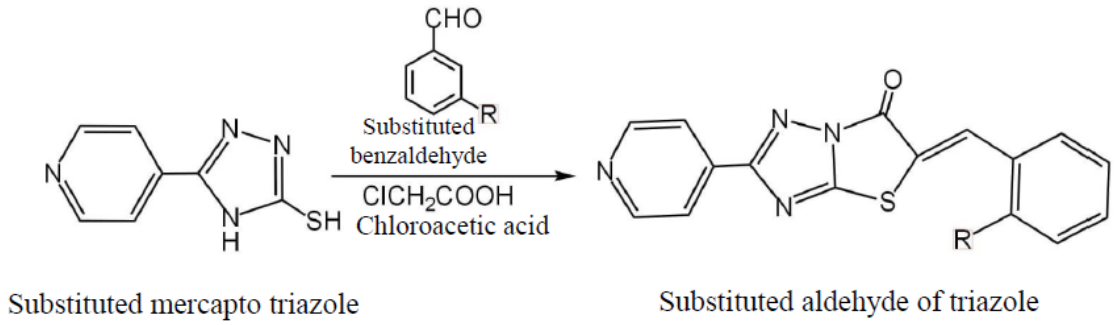


Fig.3.

- **Synthesis of 4-chloro benzaldehyde substituted 1, 2, 4-triazole derivative (from substituted mercapto triazole): Product A**

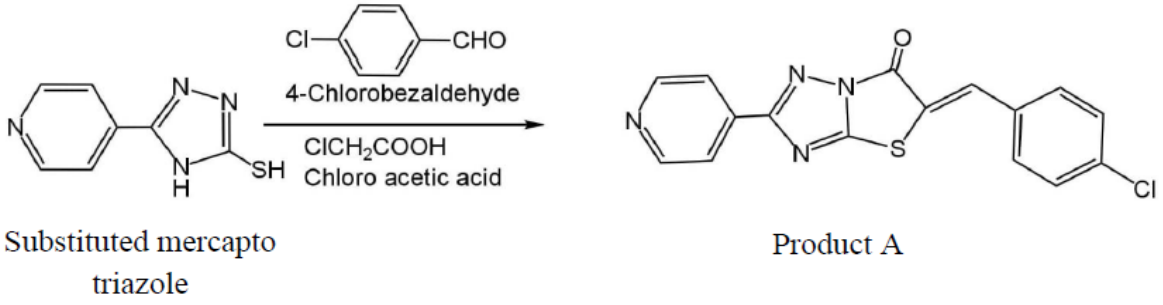


Fig.4.

- **Synthesis of Furfuraldehyde substituted 1, 2, 4-triazole derivative (from substituted mercapto triazole): Product B**

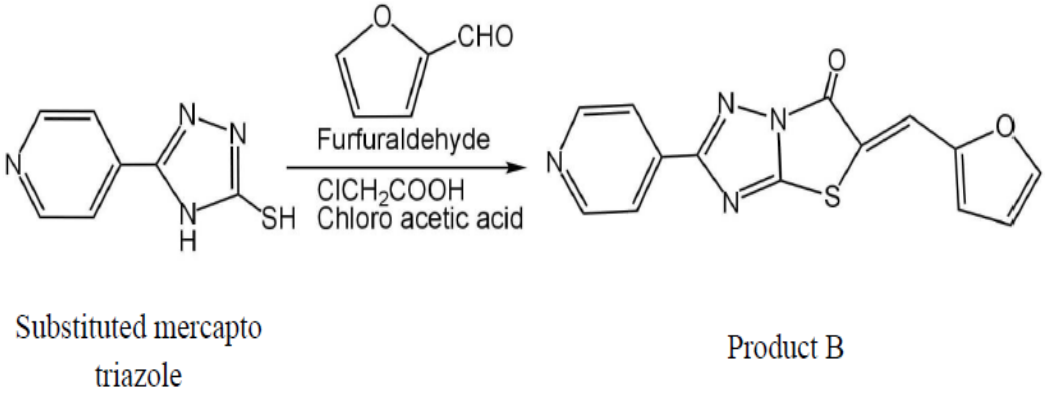


Fig.5

3. CHARACTERIZATION

I. SOLUBILITY

Table 2.

Compound	Ethanol	Acetic acid	DMSO	DMF	Acetone	Choloroform
Mercaptotriazole	YES	YES	YES	YES	YES	NO
4-Chlorobenzaldehyde	YES	YES	YES	YES	YES	YES
Furfuryldehyde	YES	YES	YES	YES	YES	YES
PRODUCT A	YES (hot)	YES (hot)	YES	YES	YES (partially)	YES (partially)
PRODUCT B	YES (hot)	YES (hot)	YES	YES	YES (partially)	YES (partially)

II. THIN LAYER CHROMATOGRAPHY

Thin Layer Chromatography (TLC) is a simple, rapid, and inexpensive analytical technique used to separate non-volatile mixtures. It involves a stationary phase, typically a thin layer of silica gel, alumina, or cellulose coated on a flat substrate (like a glass, plastic, or aluminium plate), and a mobile phase (solvent or solvent mixture) that moves by capillary action, helping in the separation of the components in a mixture based on their relative affinities.[10]

The TLC for the both product A & B were done by using TLC sheet as a stationary phase.

Mobile phase: Chloroform: Ethanol (8: 2)

Solvent: Ethanol (for dissolving samples)

TLC CHAMBER

A) INH

B) Mercaptotriazole

PRODUCT A

PRODUCT B

Retardation factor

Defined as the ratio of distance travelled by solute and distance travelled by solvent.

RF values

- For Isoniazid - Rf value = 1.7/3.8 = 0.44
- For Mercaptotriazole - Rf value = 2.4/3.8 = 0.63
- For Product A : Rf value = 1.9/3.3 = 0.57
- For Product B : Rf value = 2.4/3.9 = 0.61

III. Melting Point

The melting points of the synthesized compounds were determined by open capillary method on melting point apparatus.

- For mercaptotriazole: Melting point: 216 ^{o}C
- For Product A : Melting point: 229^{o}C
- For Product B : Melting point: 229^{o}C

IR & NMR Spectral study of synthesized compound

INFRARED SPECTROSCOPY

Infrared spectroscopy is the study of how molecules absorb infrared light and convert it into vibrations, helping to identify functional groups and molecular structures.[11]

PRINCIPLE

Infrared (IR) spectroscopy is based on the principle that molecules absorb infrared radiation at specific frequencies that correspond to the vibrational transitions of their chemical bonds.

Infrared spectroscopy and nuclear magnetic resonance studies for the synthesized compounds were done using DMSO as solvent.

NUCLEAR MAGNETIC RESONANCE

NMR is a technique used to find out the structure of molecules by observing how atomic nuclei (like hydrogen or carbon) behave when placed in a magnetic field and exposed to radiofrequency waves.

It is used for molecular structure determination, dynamic studies, and chemical analysis.

Common nuclei: Hydrogen-1(^{1}H), Carbon-13 (^{13}C), Fluorine-19 (^{19}F), Phosphorus-31 (^{31}P), etc.[12]

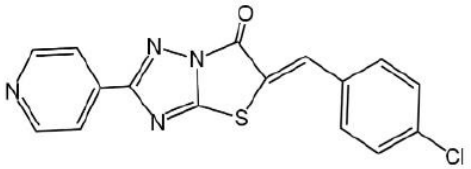
PRINCIPLE

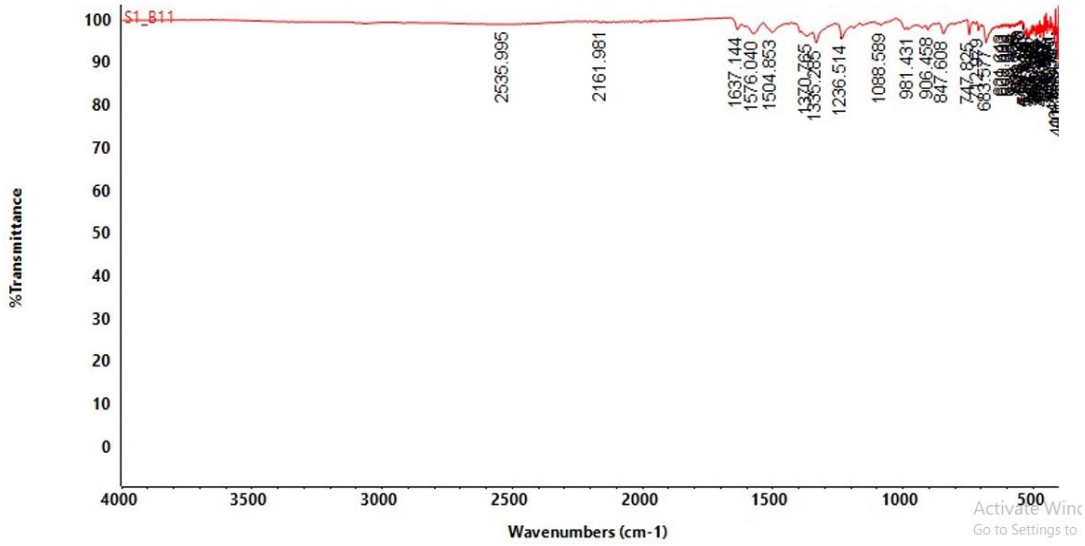
The principle of NMR is based on the magnetic properties of certain atomic nuclei. When placed in an external magnetic field, these nuclei absorb radiofrequency (RF) radiation at a specific frequency, and this absorption is used to analyze molecular structure.

Table 3.

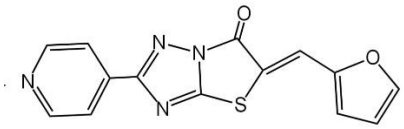
SPECTROSCOPY	COMPOUND	SPECTRAL PEAKS (c/m)	MOLECULAR NATURE
IR	PRODCUT A	1637.14	C=O (hetero aromatic)
IR	PRODCUT B	1636.95	C=O (hetero aromatic)
NMR	PRODCUT A	3.91 8.69	C-H (alkyl) C-H (hetero aromatic)
NMR	PRODCUT B	3.86 7.84	C-H (alkyl) C-H (hetero aromatic)

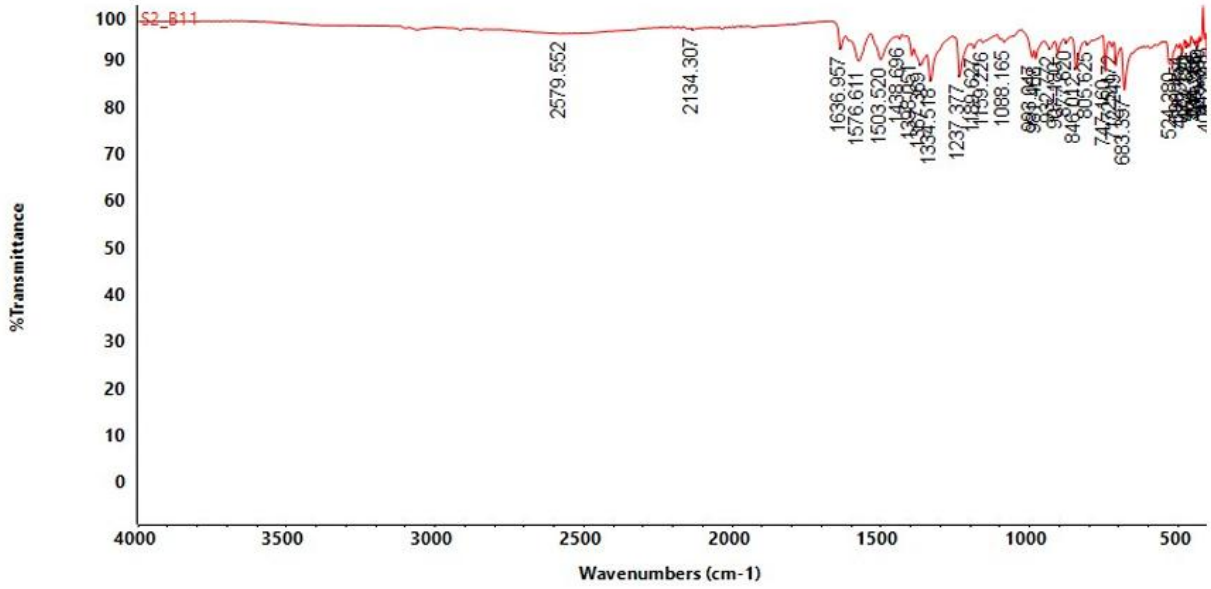
PRODUCT A: IR



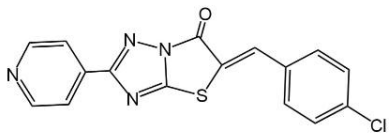


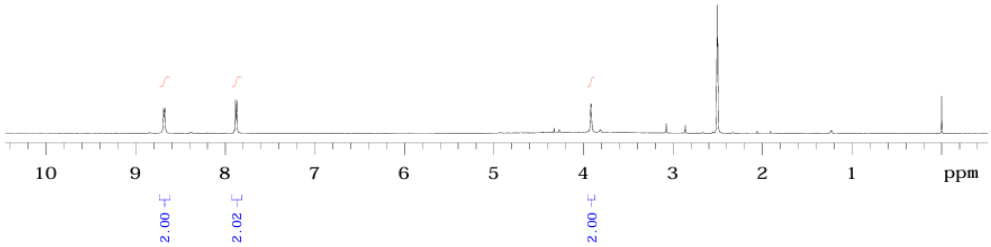
PRODUCT B: IR



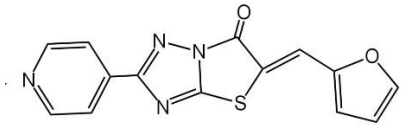


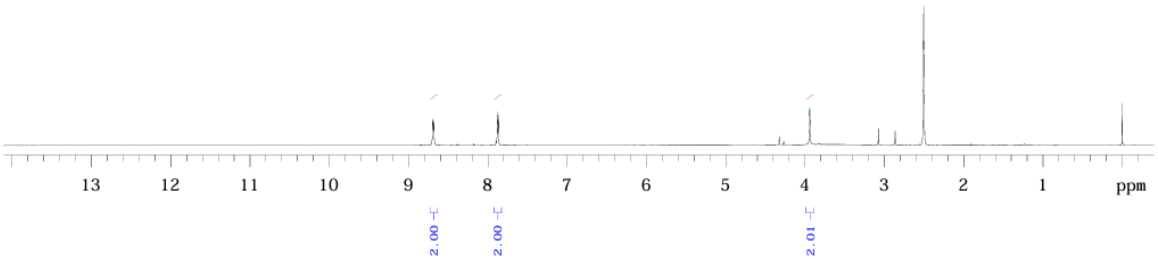
PRODUCT A: NMR





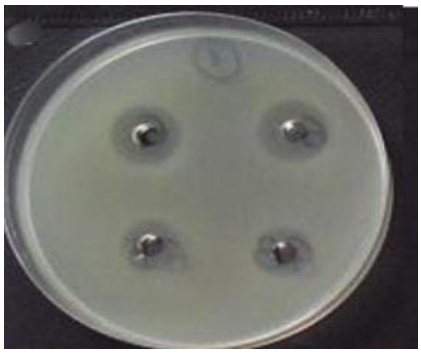
PRODUCT B: NMR



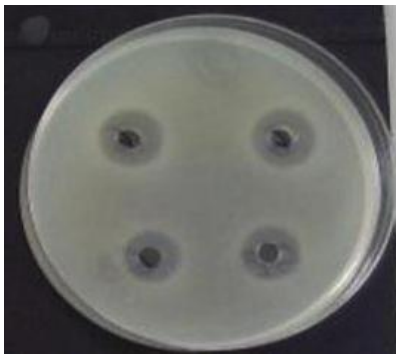


Anti-bacterial activity

- The microbial world comprises of micro-organism which are microscopic in size. But these microscopic organisms have several features that are common to higher organism.
- Bacteria, fungi (yeast and moulds) and microscopic algae are some of micro-organism. This organism can be distinguished into two broad groups such as prokaryotes and the eukaryotes.
- Eukaryotes contain nucleus and organelles (such as endoplasmic reticulum, Golgi bodies, lysosome, mitochondrion and chloroplast) whereas prokaryotes lacks above features.
- In this study the Agar well diffusion method is used for the evaluation of anti-bacterial activity



Gram +ve (Staphylococcus aureus)



Gram –ve (E.coli)

Anti-bacterial data for synthesized compounds.

COMPOUND	ZONE OF INHIBITION (in mm)		
	100 (µg/ml)	200 (µg/ml)	300 (µg/ml)
PRODUCT A	11	12	14
PRODUCT B	11	13	15
STANDARD (POVIDONE-IODINE)	12	14	16

CONCLUSION

- In the present study Triazole derivatives were synthesized. The synthesized compounds were characterized by melting point, TLC, IR, NMR spectra.
- The synthesized 1, 2, 4-triazoles were subjected to anti-bacterial activity.
- The zone of inhibition at various concentrations of synthesized compounds against various bacteria were measured by Agar well diffusion method and found that increasing in the concentration leads to increasing in the zone of inhibition. In comparing with both the compounds A&B, product B has shown more anti-bacterial activity.

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