

# Microwave Assisted Synthesis of Triazole based Scaffolds by Green Approaches and Catalytic Innovations: A Review

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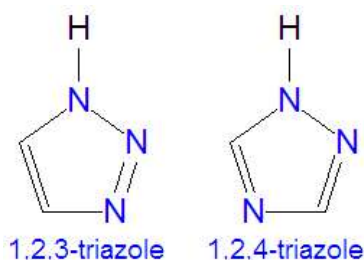
## Abstract

The microwave-assisted synthesis of triazoles has emerged as a powerful and efficient approach in heterocyclic chemistry, offering significant advantages over conventional thermal methods. Triazoles, particularly 1,2,3- and 1,2,4-triazoles, are valuable scaffolds with broad applications in pharmaceuticals, agrochemicals, and materials science. Microwave irradiation facilitates rapid and uniform heating, dramatically reducing reaction times and often enhancing yields and product purity. Among the most prominent techniques is the copper(I)-catalysed azide-alkyne cycloaddition (CuAAC), commonly known as “click chemistry,” under microwave conditions proceeds with exceptional efficiency and selectivity. The method supports green chemistry principles, frequently allowing solvent-free or aqueous-phase reactions and the use of recyclable catalysts. Diverse synthetic routes were developed for synthesis of triazole derivatives by microwave technique underscoring its role as a sustainable and high-throughput alternative in modern synthetic chemistry.

**Keywords:** cycloaddition; 1,2,4-triazole; eco-friendly; microwave reactor; thermochemical analysis etc

## INTRODUCTION

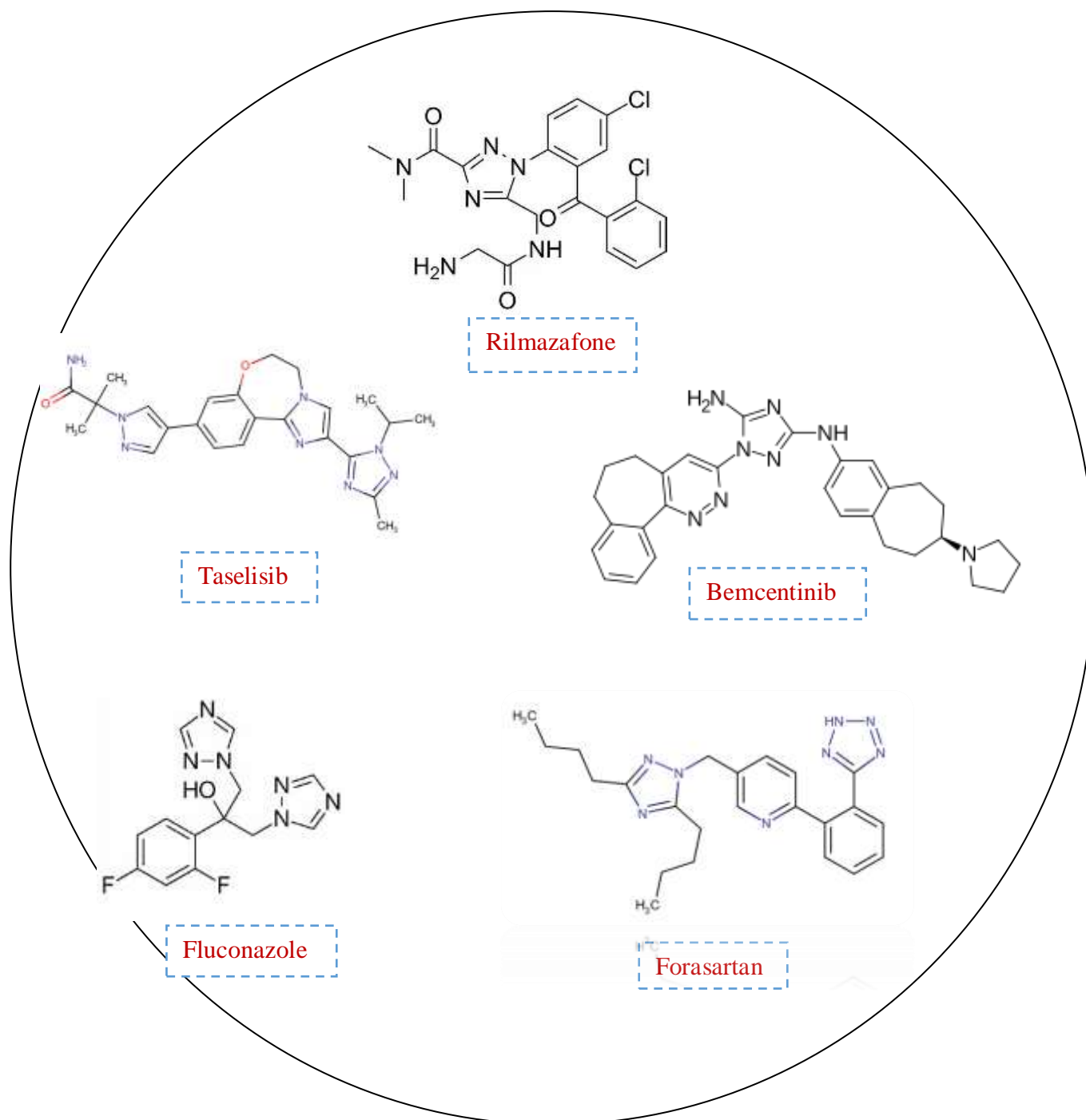
Green chemistry synthesis has found wide applicability in the synthesis of various organic compounds, particularly heterocycles, natural product analogues, and pharmaceuticals. Its utility extends to multicomponent reactions, metal-catalysed cross-couplings, and peptide synthesis. In many cases, microwave irradiation enables transformations that are otherwise sluggish or low-yielding under conventional conditions. Moreover, microwave techniques have also been applied in materials chemistry, nanoparticle synthesis, and polymer science, showcasing their versatility. For example, green synthesis of nanoparticles using plant extracts under microwave conditions offers a rapid, energy-efficient, and non-toxic alternative to traditional methods. Microwave-assisted synthesis (MAS) represents a transformative advance in synthetic chemistry that aligns strongly with the principles of green chemistry. By offering a cleaner, faster, and more energy-efficient alternative to conventional heating methods, MAS facilitates the development of more sustainable chemical processes. Its broad applicability across various domains of chemistry, from small molecule synthesis to nanomaterials, underscores its potential to shape the future of environmentally responsible chemistry. As technology continues to evolve, further integration of microwave methods into industrial-scale processes will play a crucial role in achieving greener and more efficient chemical manufacturing.



**Fig 01:** Structural isomers of Triazole

Triazoles have gained significant attention in medicinal, agricultural, and materials chemistry due to their unique stability, ability to participate in hydrogen bonding, and biological activity. Triazoles are five-membered heterocyclic compounds containing three nitrogen atoms and two carbon atoms in the ring. They exist in two main isomeric forms such as 1,2,3-Triazoles and 1,2,4-Triazoles. These isomers leading to different reactivity and applications. Triazoles can exhibit tautomerism (especially 1,2,4-triazoles), where the position of a hydrogen atom and a double bond change, influencing their reactivity. Among these two, 1,2,4-Triazole is an important part of many drugs, including antifungal treatments, anticancer agents, and some substances for microbial infections and weight loss. Notable examples are the antihypertensive drug forasartan, deferasirox for iron overload, and medications rilmazafone and potential cancer treatments bemcentinib and taselisib, antifungal agent e.g., fluconazole. Advances in virtual screening allow

exploration of chemical space but need fast drug synthesis for testing. This can be solved by creating large virtual libraries with reliable synthesis methods that require minimal preparation and are safe from using sensitive or toxic reagents<sup>[1]</sup>.

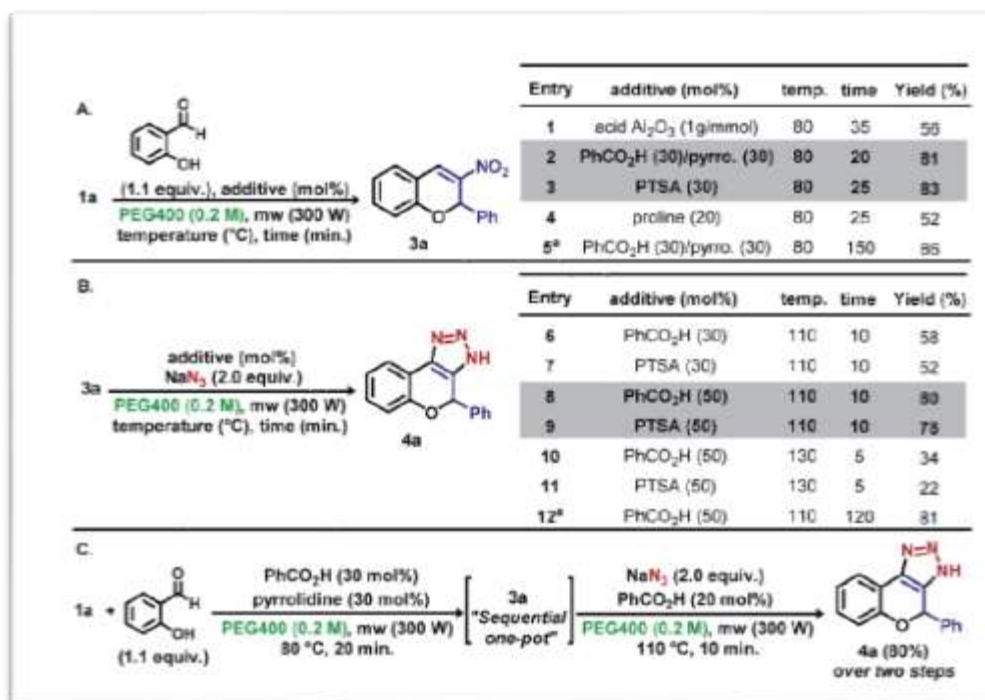


**Fig. 02:** Various drugs containing triazole scaffold

Rational design for novel molecules involved selecting protein-ligand complexes and clustering ligands. The compounds were synthesized using a microwave-assisted method with reactions like Ullmann-Goldberg, N-propargylation, Mannich addition, Friedel-Crafts, and 1,3-dipolar cycloadditions. This microwave approach was efficient, yielding 73–93% of all novel compounds. Additionally, a thermochemical analysis and optimization were done, along with reactivity indexes such as electronic chemical potential, chemical hardness, and electrophilicity, to explore the link between structure and energetic behaviour<sup>[2]</sup>.

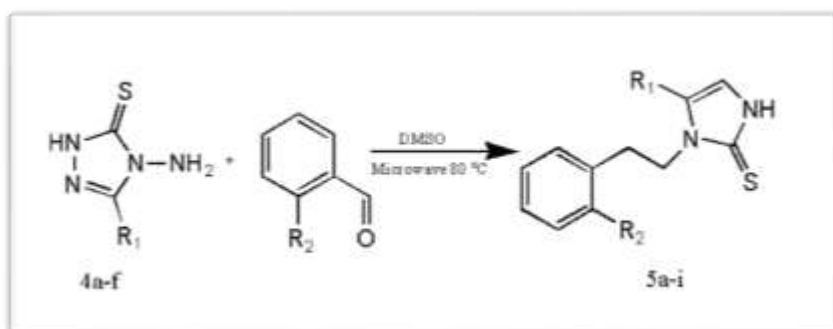
#### SYNTHETIC APPROACHES FOR TRIAZOLES SCAFFOLD BY MICROWAVE ASSISTED METHOD

- **Tania M *et al.***, have synthesized different triazole scaffold derivatives(4a) by microwave irradiation technique by taking sodium azide and PEG400 were used as the solvent in a reaction under microwave conditions at 300 W power. The reaction lasted for 10 minutes at 120 °C temperature condition, resulting in a complex mixture of various products<sup>[3]</sup>.



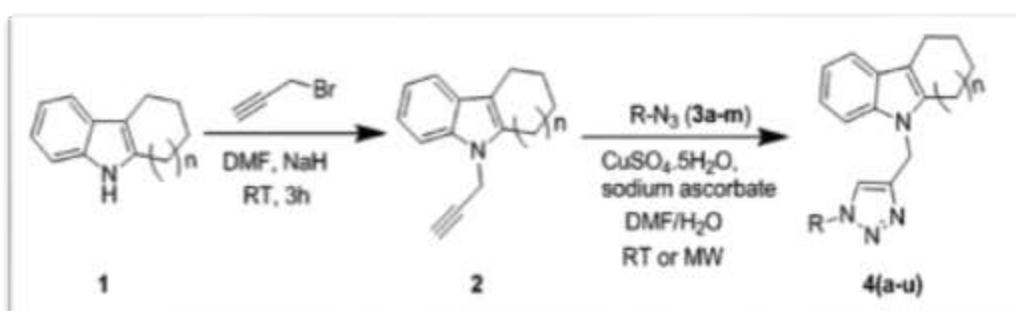
Scheme 1

- **Mahdi Shirmohammadi *et al.***, have reported novel triazole derivatives. For this reaction, substituted amino triazole was mixed with an equal amount of substituted benzaldehyde, along with a few drops of DMSO. This mixture was then heated in a microwave at 80 °C using a specific lab reactor. After the reaction, it was allowed to cool, and 20 mL of water was added. The resulting material was filtered, washed with hot water, and finally recrystallized in methanol <sup>[4]</sup>.



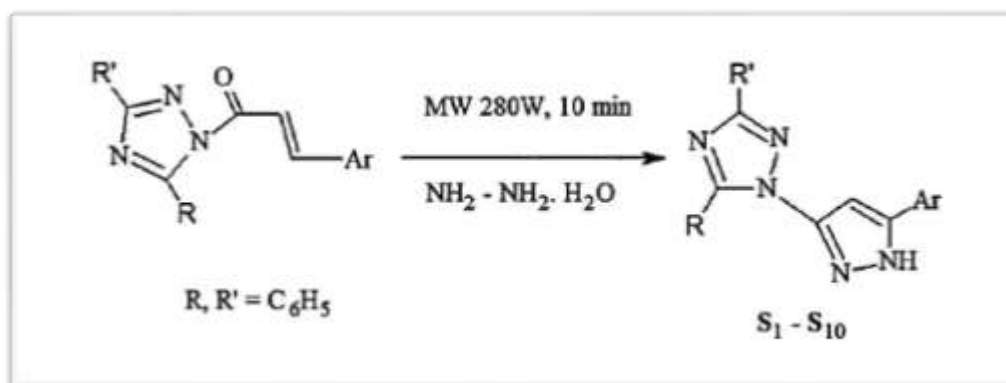
Scheme 2

- **Dongamanti Ashok *et al.***, synthesized novel compounds by microwave method. Cyclohexanones were reacted with phenyl hydrazine to create various tetrahydro carbazoles. This was followed by N-alkylation with propargyl bromide, using sodium hydride as a base in DMF to yield 9-(prop-2-yn-1-yl)-2,3,4,9-tetrahydro-1H-carbazole. A click reaction was then performed on the alkynes with different aromatic azides to produce N-substituted 1,2,3-triazolyl methyl indole derivatives. To enhance yield and reduce reaction time, optimization of the copper-catalysed cycloaddition was conducted, testing various catalysts and solvents. The best results were achieved with CuSO<sub>4</sub> and sodium ascorbate in a DMF/H<sub>2</sub>O mixture. Microwave irradiation provided higher yields and shorter reaction times compared to conventional methods <sup>[5]</sup>.



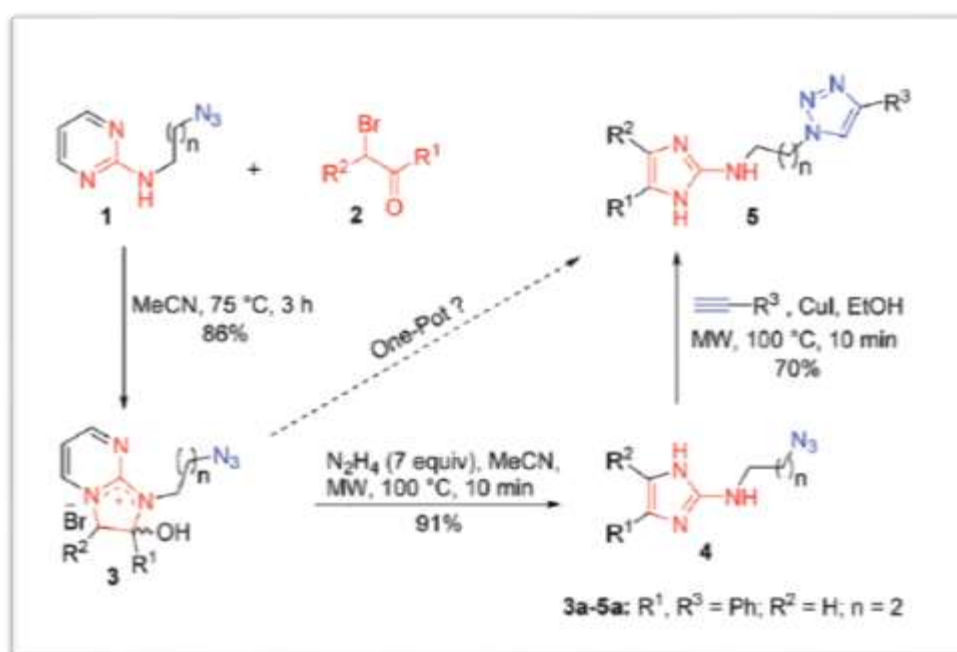
Scheme 3

- **Khanage *et al.***, have synthesized 1- [5-(substituted aryl)-1H-pyrazol-3-yl]-3,5-diphenyl-1H-1,2,4-triazole derivatives (S1-S10). The desired compounds were synthesized by the cyclization of 1-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-3-(substituted aryl) prop-2-en-1-one (Chalcones, 0.01 mol) and hydrazine hydrate (0.01 mol) in the presence of a small amount of glacial acetic acid. The reaction mixture was subjected to microwave irradiation for 10 minutes at 280 W power. After the completion of reaction, the precipitate of product obtained was washed with cold water and dried. The crude product was recrystallized from ethanol: water mixture (1:1). All the compounds were obtained in good yield. Then, the chalcones were converted into pyrazoles combined with 1,2,4-triazole using hydrazine hydrate in an acidic environment, good yield was obtained [6].



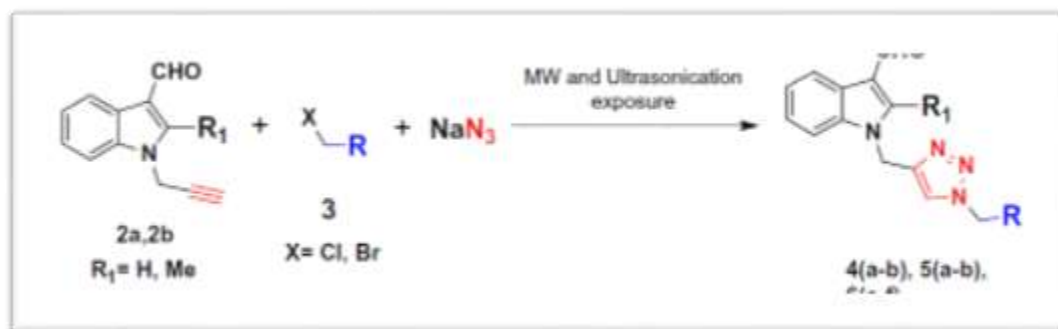
Scheme 4

- **Hans Steenackers *et al.***, were synthesized novel compounds (3a-5a). A mixture of N-(3-azidopropyl) pyrimidin-2-amine and phenacyl bromide was heated in methyl cyanide at 75 °C for 3 hours, creating a 2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a] pyrimidin-4-ium salt. This salt then reacted with hydrazine hydrate, leading to the formation of N-(3-azidopropyl)-1H-imidazol-2-amine. Following this, a CuAAC reaction was performed using phenylacetylene and CuI as a catalyst under microwave irradiation at 100 °C for 10 minutes, resulting in the desired product with a 70% yield [7].



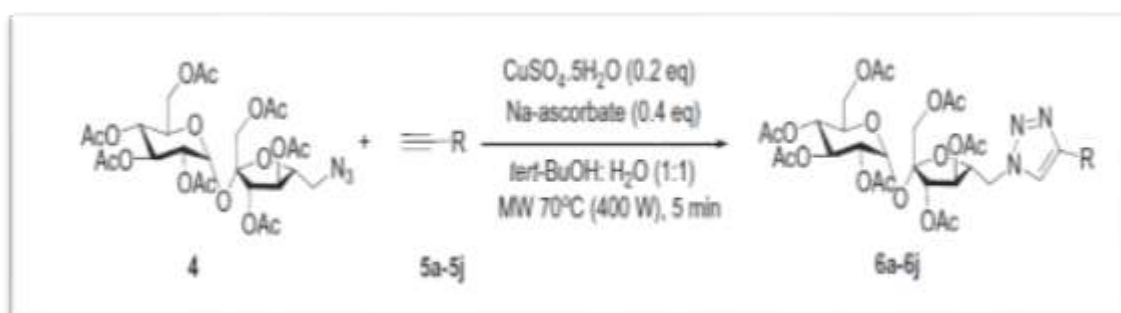
Scheme 5

- **Jaydeep A. Mokariya *et al.***, and his co-workers reported by performing a green synthesis. In a 50-mL round-bottom flask, equal amounts of 2-substituted-1-(prop-2-yn-1-yl)-1H-indole-3-carbaldehyde, 2-chloroacetic acid or 2-chloroethyl acetate, and sodium azide were mixed in DMF with powdered copper iodide. This mixture was then heated in a microwave at 100 W for 15–30 minutes. After the reaction was complete, as shown by TLC, the solution was cooled to room temperature. Water was added slowly while stirring, causing a solid to form. This solid was filtered, washed with saturated sodium bicarbonate, dried, and then purified using chromatography with ethyl acetate and hexane as the solvent [8].



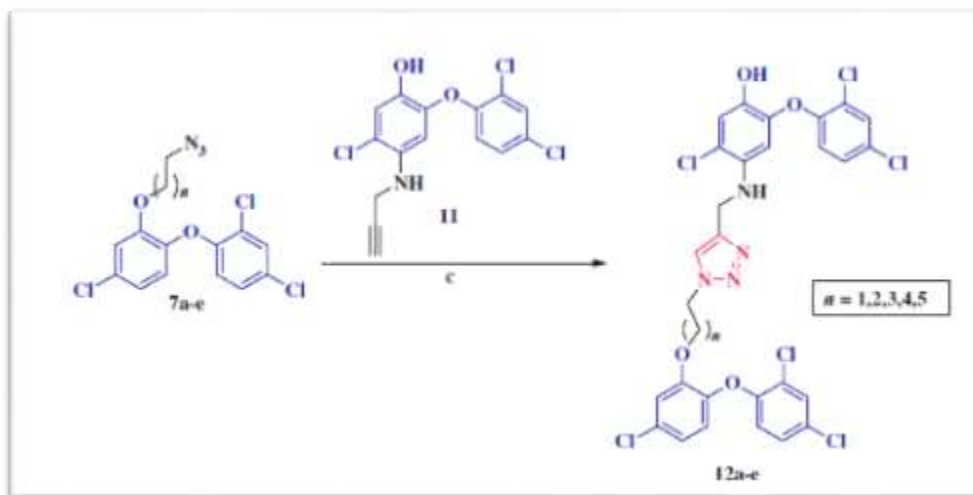
Scheme 6

- **Taterao M. Potewar *et al.***, have synthesized 1,2,3-triazole–sucrose derivatives, a model reaction was done using compound 4 (1,2,3,3',4,4',6-hepta-O-acetyl-6'-azido-6'-deoxy-sucrose) and phenyl acetylene 5a with  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and sodium ascorbate in a mixture of tert-butanol and water. The reaction occurred at temperatures of 35, 50, 60, and 70 °C using both conventional heating and microwave irradiation. The optimal results were at 70 °C, yielding product 6a in 3 hours with conventional heating and in 5 minutes under microwave irradiation, achieving a high yield of 91% in both cases. Raising the temperature above 70 °C did not improve the results. The microwave reactions were conducted in a specialized reactor, which allowed for rapid energy transfer and maintained the correct temperature, preventing substrate decomposition. As the set temperature was reached, power was adjusted to keep the temperature stable, making the reaction conditions based on temperature rather than magnetron power. Using these optimized conditions, various alkynes were reacted with 6'-azido sucrose to produce several 1,2,3-triazoles in excellent yields and short times <sup>[9]</sup>.



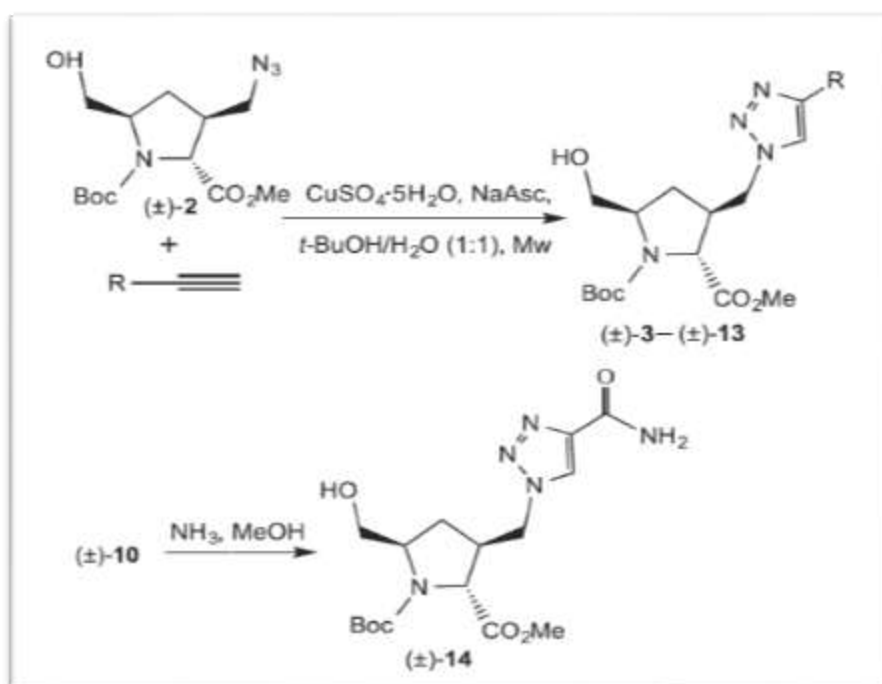
Scheme 7

- **Shekhar *et al.***, were synthesized substituted triazoles (12a-e). The process for making O-alkyl azido TCS derivatives 7a–e started with O-alkylation of TCS (1) using dibromo alkane in DMF at 100°C for 20 minutes, producing O-alkylbromotriclosan 6a–e. This was followed by a reaction with sodium azide in DMF at 120°C for 10 minutes, all done in a microwave reactor. After confirming the reaction was complete with TLC, the mixture was diluted with water and extracted with dichloromethane three times, then washed with brine and dried using anhydrous sodium sulphate. The drying agent was removed by filtration, and the filtrate was evaporated under reduced pressure. The crude product was purified using flash chromatography with silica gel and a solution of ethyl acetate and hexane. Good yields of the final compounds were achieved. Then, the precursors 3/5/11 and O-alkylazidotriclosan derivatives 7a–e were mixed in DMSO, with CuI and DIPEA added for the reaction. This mixture was stirred for 10 minutes at 100°C in a microwave reactor. After monitoring the reaction's completion by TLC, the crude product was extracted using ethyl acetate, brine, and EDTA solution. The organic layer was dried with sodium sulphate and concentrated under reduced pressure to produce the desired compounds 8a–e, 9a–e, and 12a–e, which were then purified through flash chromatography using an ethyl acetate–hexane mixture <sup>[10]</sup>.



Scheme 8

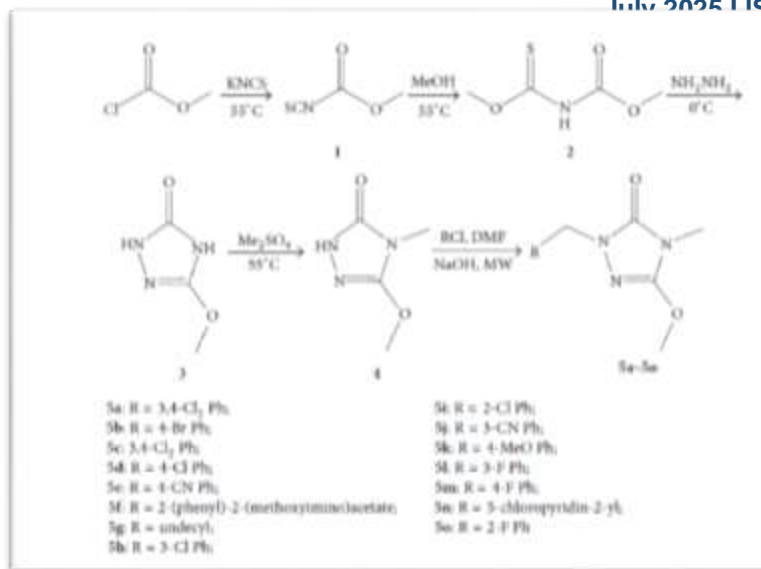
- **Joana Ferreira da Costa *et al.***, reported to improve the yield and reduce reaction times for synthesizing compound (±)-3, they have treated phenylacetylene with azide (±)-2 using  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and sodium ascorbate in a  $t\text{-BuOH}/\text{H}_2\text{O}$  mixture. Heating the reaction in a microwave at  $70^\circ\text{C}$  for 30 minutes produced triazole (±)-3 with a 92% yield. This method effectively created the 4-substituted-1,2,3-triazole moiety. The outlined conditions led to a smooth cycloaddition, yielding a single regio isomer [(±)-3e (±)-13]. Lastly, compound (±)-14 was synthesized by treating compound (±)-10 with methanolic ammonia<sup>[11]</sup>.



Scheme 9

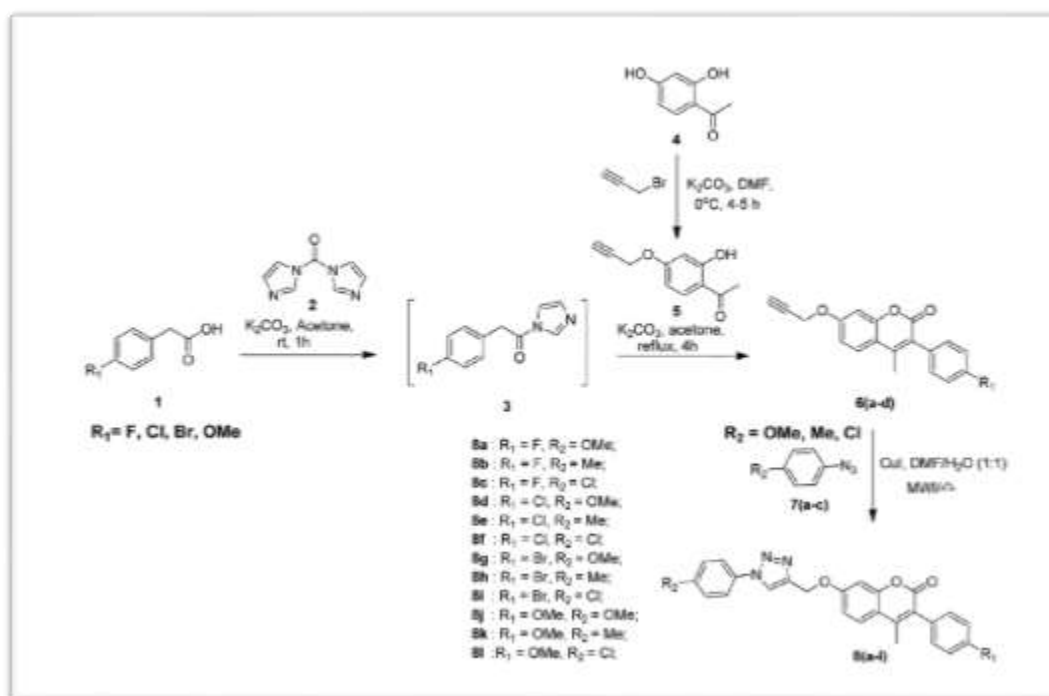
- **Na-Bo Sun *et al.***, have synthesized novel compounds (5a-5o). The synthesis of intermediates 1 and 2 begins by dissolving potassium thiocyanate and pyridine in methyl isobutyl ketone. Methyl chloroformate was added dropwise at  $55^\circ\text{C}$ , and the mixture was stirred for 4 hours. Methanol was added and stirred for another 16 hours. The mixture was then washed, filtered, and the crude product was collected, yielding an 80% white solid. For intermediate 3, a solution of intermediate 2 in methanol was treated with hydrazine and KOH at  $0^\circ\text{C}$ , then stirred at  $30^\circ\text{C}$ . The product was recrystallized to yield white crystals at 78%. To synthesize intermediate 4, intermediate 3 and  $\text{K}_2\text{CO}_3$  were reacted in acetonitrile with dimethyl sulphate at  $55^\circ\text{C}$ . Then by the utilisation of CEM Discover Focused Synthesizer, thioether 5 was synthesized by reacting intermediate 4, an alkyl chloride, and sodium hydroxide in DMF at  $90^\circ\text{C}$  for 15 minutes, after which the product was cooled and recrystallized<sup>[12]</sup>.





Scheme 10

- **Ravinder Dharavath *et al.***, have synthesized novel compounds 8(a-i) by employing microwave irradiation method. The synthetic process starts by activating substituted phenyl acetic acid with 1,1-carbonyldiimidazole and potassium carbonate in acetone at room temperature for one hour to create an intermediate. Next, alkyne-substituted hydroxy acetophenone is produced by propargylation of 2,4-dihydroxyacetophenone with potassium carbonate in DMF and then combined with the intermediate under reflux for four hours to form 3-aryl-substituted coumarin compounds. Lastly, these coumarin intermediates undergo a copper(I)-catalysed cycloaddition with aryl azides using copper iodide and DMF/H<sub>2</sub>O to yield coumarin-containing 1,2,3-triazole compounds [13].



Scheme 11

- **Sobhi M. Gomha *et al.***, their study focused on the reactivity of hydrazone derivatives, which are important for creating many heterocyclic compounds. The researchers treated (2-methyl-1H-indol-3-yl)-3-acid hydrazide with ethyl 2-(N-phenylhydrazono)-3-oxobutanoate in DMF using microwave heat, along with a small amount of HCl. This reaction produced 3-[(3-methyl-4-phenylhydrazono-5-oxopyrazolin-1-yl) carbonyl]-2-methyl-1H-indole by eliminating ethanol and water [14].

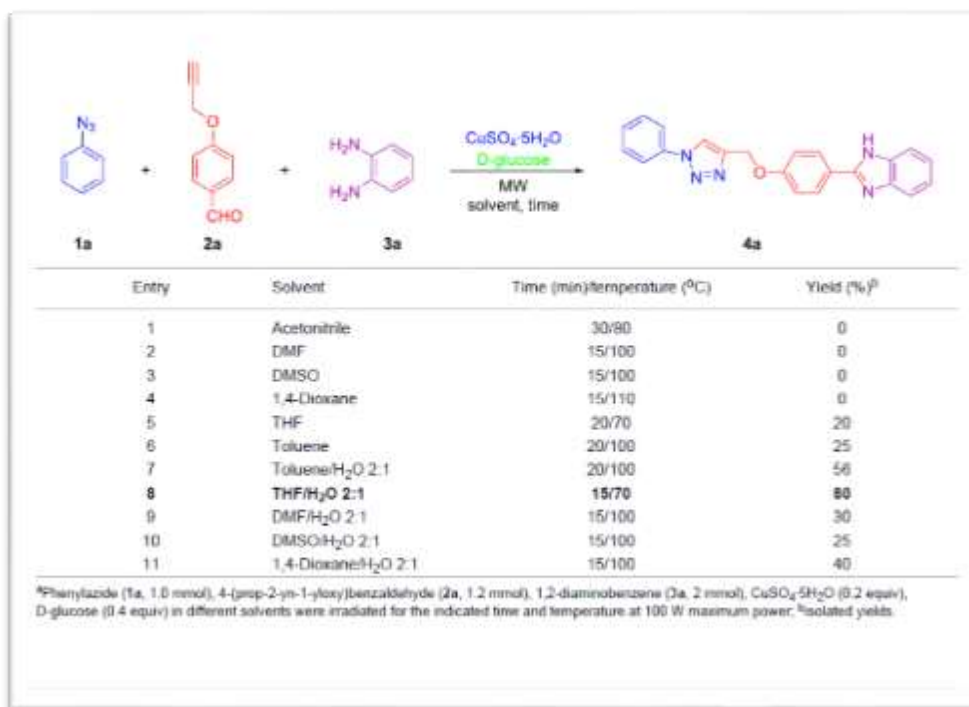


➤ **Giuseppe Caliendo *et al.***, have synthesized novel series of compounds (15a-23a) and 15b-23b). To prepare 1- and 2- [2-, 3- or 4-[4-(R)1-piperazin-yl] alkyl] (4-benzoyl)-1,2,3-triazoles, start by mixing the appropriate 1 or 2-(chloroalkyl)-4-benzoyl-1,2,3-triazole with NaI in DMF kept reflux for 30 min, add 4-R-substituted piperazine and K<sub>2</sub>CO<sub>3</sub>. Next, transfer the mixture to a reaction vessel, set the required microwave conditions, and then cool the mixture. Concentrate it, dissolved the residue in water, and extracted it with CH<sub>2</sub>Cl<sub>2</sub> and organic layer was dried, concentrate it again, and they have performed chromatography to obtain the desired 1-isomers or 2-isomers <sup>[15]</sup>.



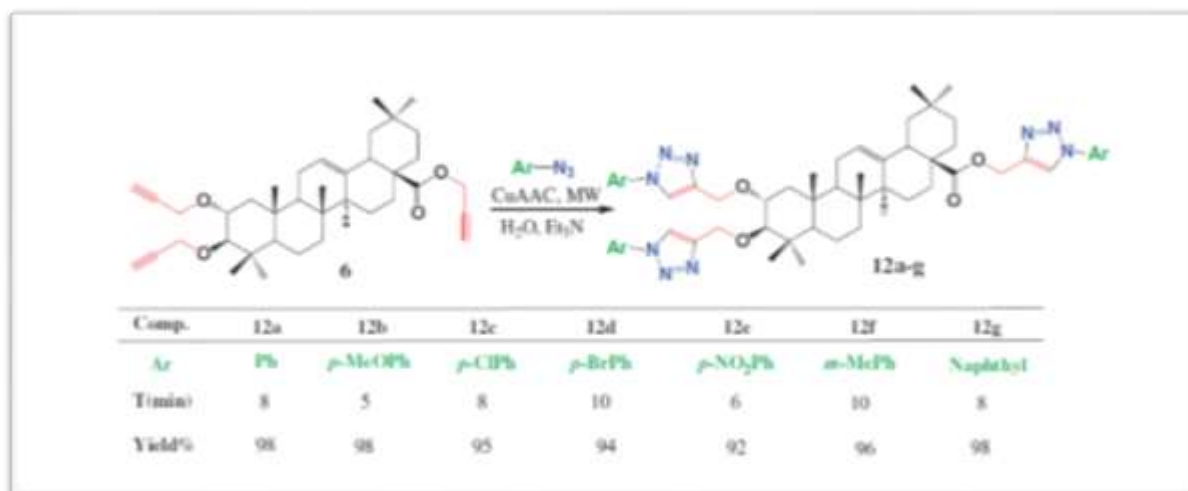
Yogesh Kumar *et al.*, reported their study investigated the reaction between phenylazide, 4-(prop-2-yn-1-yloxy) benzaldehyde, and 1,2-diaminobenzene. It was found that using polar solvents like acetonitrile, DMF, DMSO, or 1,4-dioxane did not yield any products. However, microwave irradiation in non-polar solvents like THF or toluene led to the product formation, with yields of 20% and 25%. Aqueous solvent systems improved yields, especially a THF/H<sub>2</sub>O mixture, due to better solubility of CuSO<sub>4</sub>, while polar solvents caused aggregation and reaction failure [16].





Scheme 14

- **Karim Chouaib *et al.***, have synthesized novel triazole derivatives by the utilisation of Cu catalysed reaction. Their study focused on using CuAAC for creating tri-1,4-disubstituted triazolyl compounds. Unlike dipolarophiles 2-5, tri-alkyne 6 is fully water-soluble. Researchers have examined how tri-alkyne 6 reacted with phenylazide 7a when using triethylamine and different amounts of CuI catalyst under microwave heating in water. They found that adding 1 equivalent of CuI was crucial for achieving the best yield of tri-1,4-disubstituted triazolyl 12a quickly. With optimized conditions, they have treated dipolarophile 6 with various aromatic azides, achieving yields between 92% and 96% in just 5-10 minutes <sup>[17]</sup>.



Scheme 15

## CONCLUSION

The advent of microwave-assisted organic synthesis (MAOS) has revolutionized the synthesis of heterocyclic compounds, particularly triazoles, by offering a greener, faster, and more efficient alternative to conventional heating methods. This technique has significantly reduced reaction times, enhanced yields, and minimized the need for harsh reagents and solvents factors that are crucial in both academic and industrial settings. The thermal efficiency and uniform heating provided by microwave irradiation promote cleaner reactions and often allow for catalyst- or solvent-free conditions, aligning well with the principles of green chemistry. Triazoles, owing to their wide spectrum of biological and pharmaceutical activities—including antimicrobial, anticancer, antiviral, and anti-inflammatory properties continue to be a focal point in drug discovery and material science. Microwave-assisted strategies have proven particularly effective for synthesizing both 1,2,3- and 1,2,4-triazole scaffolds through various cycloaddition and

condensation reactions, often under mild and eco-friendly conditions. Based on this literature survey, all the newly synthesized triazole derivatives were found maximum yields as compared to conventional method of synthesis in a very short duration of time and their compounds were also characterised by FT-IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and Mass spectrometry, thus obtained excellent results. Despite its advantages, challenges such as scale-up limitations, equipment cost, and substrate-specific optimization still require further exploration. However, ongoing developments in microwave reactor design and hybrid techniques suggest promising improvements. Thus, microwave-assisted synthesis represents a highly valuable tool in modern heterocyclic chemistry, and its continued application and refinement will undoubtedly accelerate the development of triazole-based compounds with enhanced efficacy and sustainability.

## ACKNOWLEDGMENT

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## CONFLICTS OF INTEREST

There are no conflicts of interest.

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