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# Recent advances in microwave-assisted synthesis of triazoles and their derivatives: a green approach toward sustainable development methods

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Triazole, a nitrogen-containing five-membered heterocycle with two isomeric forms, 1,2,3-triazole and 1,2,4-triazole, has proven to be a valuable component in the pharmaceutical domain. Owing to its widespread utility in drug development, pharmaceutical and medicinal chemistry, several synthetic methods have been explored, such as different catalytic systems, solvents, and heating methodologies in recent years. However, some methods were associated with several limitations, such as harsh reaction conditions, high temperatures, low atom economy, and long reaction times. Conversely, the ongoing demand from the chemical industry has led to increased attention on overcoming these limitations and developing sustainable laboratory methods. In recent years, the microwave heating method in organic synthesis has evolved as a new, environmentally friendly approach with benefits such as atom economy, reduced use of hazardous chemicals, safer chemical design, few derivatives and enhanced energy efficiency. This review summarizes recent progress in microwave-assisted synthesis of triazoles (1,2,3-triazole and 1,2,4-triazole), with a comparative analysis between conventional methods and microwave-assisted methods in terms of reaction time, yield, green synthesis, sustainability and other relevant factors.

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## Introduction

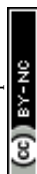
Heterocycles are important components in most commercially available drugs because of their ability to manipulate lipophilicity, hydrogen bonding, polarity, pharmacokinetic, pharmacological, physicochemical and toxicological properties.<sup>1</sup> A potent method for designing novel bioactive molecules is directly and indirectly associated with the synthesis of various heterocyclic derivatives.<sup>2</sup> Therefore, significant interest has been generated in the synthesis of various heterocycles, multi-heterocycles and hybrid heterocyclic molecules in recent years.<sup>3,4</sup> Among the diverse range of heterocyclic entities, nitrogen-containing heterocyclic molecules have received massive attention because of their role as core structures in numerous natural products and bioactive molecules, such as vitamins, antibiotics, hormones, glycosides, and alkaloids, which are important for human and animal health. Thus, nitrogen-containing heterocycles are specifically regarded as “privileged” structures for synthesis and development of novel drug molecules.<sup>5,6</sup> Triazoles, with two isomeric forms, 1,2,3-triazole and 1,2,4-triazole derivatives, are an important class of

molecules due to their biological importance and potential as drug development agents.<sup>7</sup> Due to the diverse pharmacological spectrum of both isomeric forms of triazoles, they have emerged as viable candidates in the drug development process over the past few decades. Generally, triazoles and their derivatives are uncommon in nature; hence, synthetic methodologies for molecules containing triazole have been widely explored for the formation of pharmaceutical molecules.<sup>8</sup> Strong chemical stability (usually inert to reducing and oxidizing agents), dipole moment, rigidity and hydrogen bonding capabilities are some favorable characteristics of the triazole ring.<sup>9</sup> It was found that the production of triazole-containing molecules using conventional methods is associated with longer reaction times, poor yields and harsh reaction conditions. In view of all these limitations, efforts to discover novel methodologies and techniques for the synthesis of complex triazole-containing heterocyclic molecules have been continuously pursued over the past few decades.<sup>10–17</sup>

In recent decades, the concept of sustainability has received significant attention both in industry and society, with the notion of “meeting the needs of the present generation without compromising the future generation’s needs”.<sup>18,19</sup> In the progress of sustainable development, the principle of green chemistry addresses the fundamental scientific challenges of protecting both the environment and human health. Therefore, modern green chemistry techniques have gained increasing popularity as non-conventional methods for rapid organic transformations. It was found that non-classical techniques

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adopting green chemistry principles could reduce/eliminate the formation of hazardous substances and the use of traditional hazardous volatile organic solvents. Among the various non-classical methodologies, microwave-assisted synthesis is one of the promising green methodologies for the rapid synthesis of different organic entities.<sup>20</sup>

Chemical synthesis has been traditionally carried out by conductive heating with the aid of an external heat source, such as a hot plate, heating mantel, water bath, sand bath and oil bath.<sup>21</sup> In traditional methods, generally heat must first pass through the vessel/container walls before it can reach the solvent and reactants (Fig. 1a). This methodology depends on the thermal conductivities of several components that must be stabilized; thus, this method of transferring energy into the system is cumbersome and ineffective. Additionally, the temperature of the reactor/reaction vessel was higher than the reaction mixture until adequate time had elapsed to allow the reaction vessel and contents inside the vessel to establish thermal equilibrium, which took more time. Additionally, conductive heating impairs the chemist's capacity to control the process. Subsequently, labor-intensive extra efforts are required to eliminate the heat source after the completion of the reaction, and cooling must be applied to reduce the bulk internal temperature.<sup>22</sup> Moreover, microwave heating is a completely different approach. As shown in Fig. 1b, the direct connection between the microwaves and molecules in the reaction mixture causes a sharp temperature rise. The process operates independently of the thermal conductivity of the vessel materials. Consequently, it achieves immediate, concentrated heating of substances responsive to either ionic conduction or dipole rotation.<sup>23–25</sup>

In general, microwave heating has several benefits that are closely related to green chemistry concepts.

- Reaction times can be significantly shortened (a few minutes or seconds) compared to traditional heating.
- Remote energy introduction is possible without physical contact between the substrates and the heating source.
- The energy inputs received by the sample can be stopped as soon as the power is turned off.
- A slower rate of thermal inertia compared with traditional conductive heating is observed.

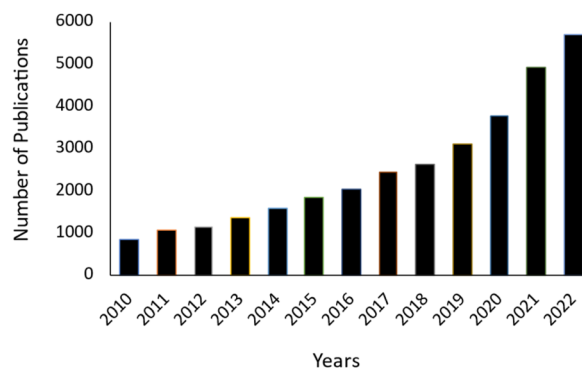


Fig. 2 Synthesis of microwave-assisted organic synthesis: progress in research papers. Data were collected using the following key words: microwave-assisted organic synthesis, organic synthesis using a microwave, microwave-controlled organic synthesis, etc.

- Energy is distributed throughout the product's mass rather than at the surface.
- If microwaves can strongly couple with some components, heating rates can drastically increase.
- This method is easily applied to parallel or sequential synthesis.
- It provides a clean, mild, easier workup procedure; greater selectivity; convenient, spontaneous reaction procedure; catalyst-free condition; regio- and stereo-selectivity and utilization of ecofriendly solvents.

These benefits are important for green and sustainable chemistry because they could boost productivity, improve safety in various ways and eliminate or reduce waste formation through more efficient processing. Therefore, interest in the microwave-assisted synthesis of heterocyclic moieties has incessantly increased because of its efficacy in all types of chemical reactions, including cycloadditions, additions, eliminations, fragmentations, substitutions and multicomponent reactions, which was witnessed as extraordinary growth in the form of studies conducted in the last few years (Fig. 2). As shown in Fig. 2, ample numbers of research articles have been published since 2010 on the synthesis of tetrazole derivatives based on a microwave-assisted approach as a green protocol. In this review, we

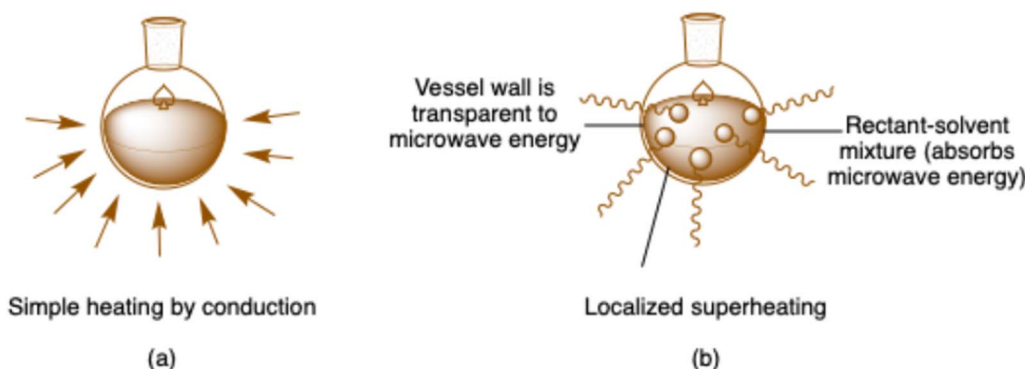
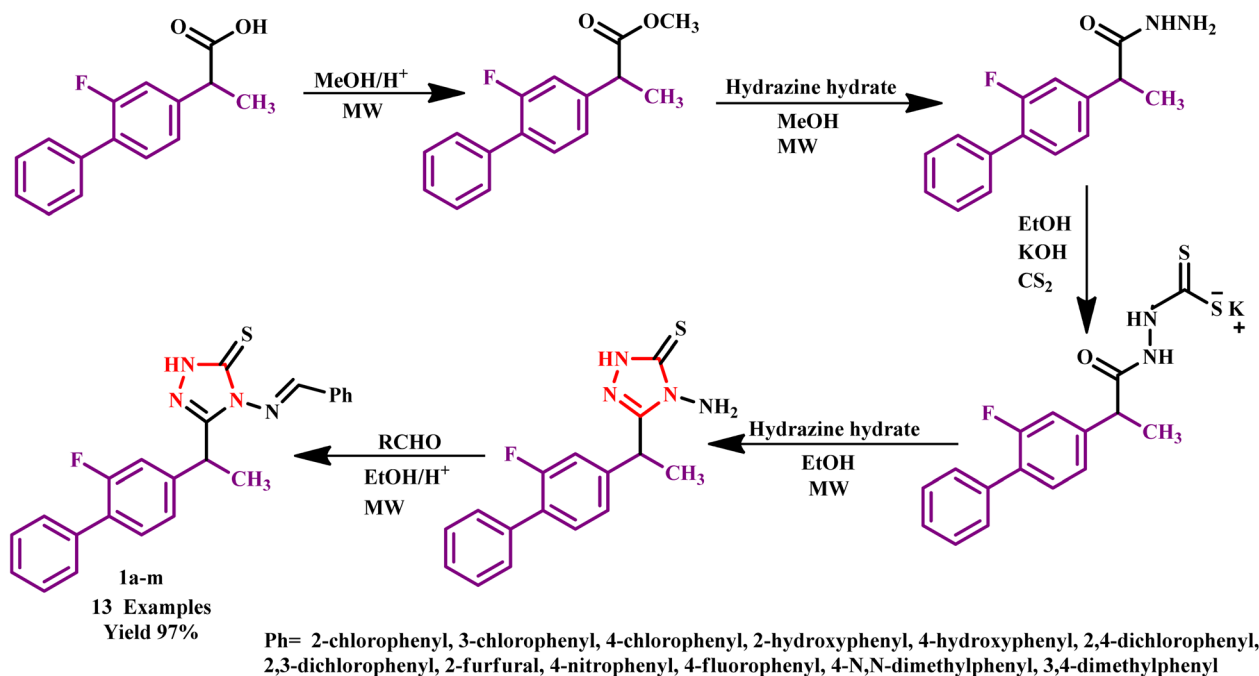


Fig. 1 (a) Illustration of reaction mixture heating using the traditional heating method and (b) reaction mixture heating via microwave.





Scheme 1 Synthetic route of 4-(benzylideneamino)-3-(1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione derivatives (1a-m).<sup>7</sup>

summarize the recent progress (from 2010 to 2023) in microwave-assisted triazole (1,2,3-triazole and 1,2,4-triazole) synthesis.

## Microwave-assisted synthesis of 1,2,4-triazole and derivatives

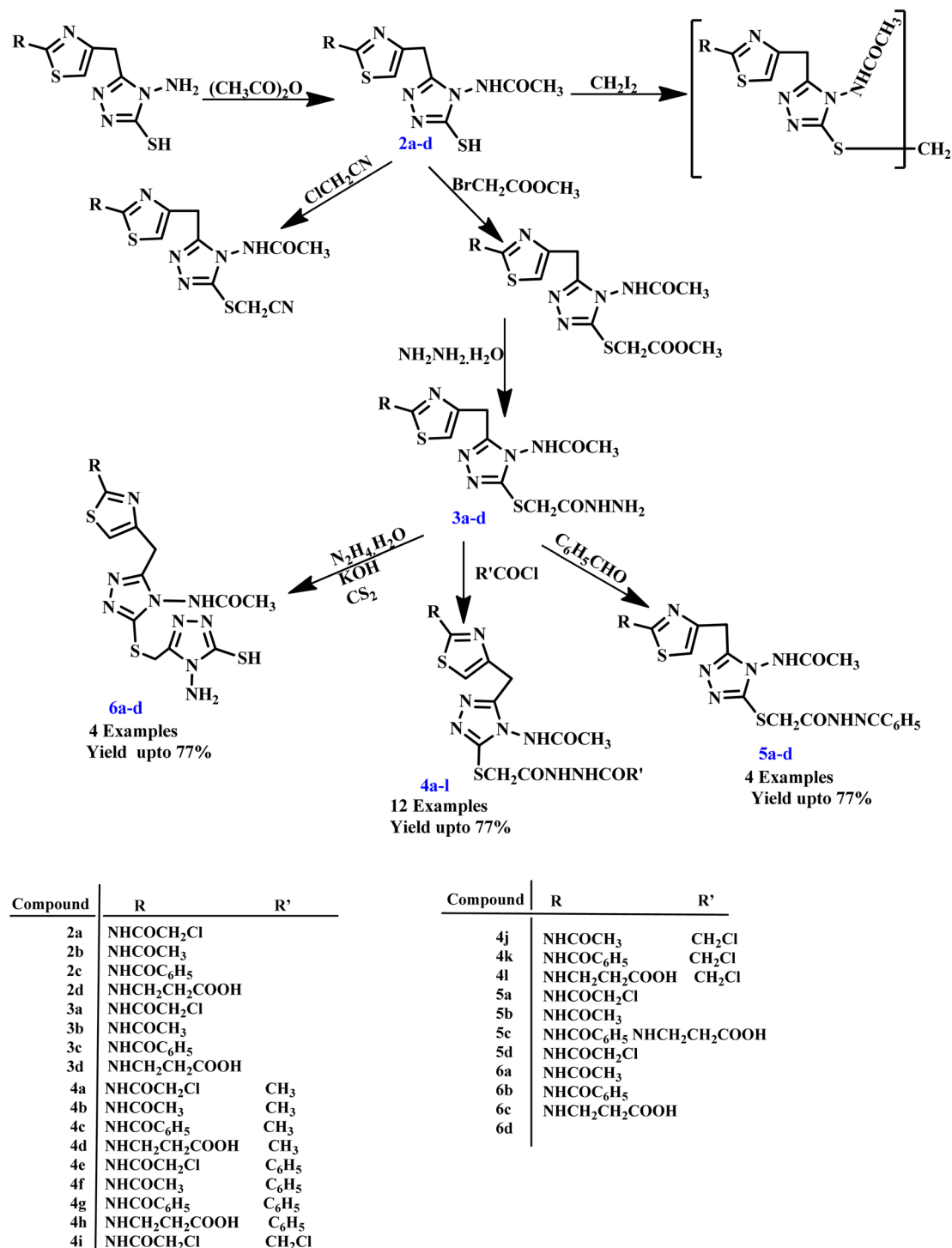
The 1,2,4-triazole is one of the isomers of triazole that has been widely explored in drug developments owing to its characteristic properties, such as antibacterial, antitubercular, anti-fungal, anti-inflammatory, analgesic, anti-tumor, antiviral, anticonvulsant, antidepressant, insecticidal and influence the central nervous system.<sup>26–30</sup> In addition, the ambident nucleophilicity of these moieties makes them excellent starting materials for the synthesis of several intriguing N- and S-bridged heterocycles.<sup>31</sup> For example, Zaheer *et al.* synthesized a series of 4-(benzylideneamino)-3-(1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione derivatives (1a-m) via microwave-assisted (MW) condensation reaction. In the condensation process, the use of MW was more effective in the reaction time minimum compared to the traditional heating method with the advantage of green reaction conditions. It was observed that the reaction was completed within 10–25 minutes with 97% yield under MW radiation, while in the conventional method, it takes 290 minutes to complete with 78% yield<sup>7</sup> (Scheme 1). It was also reported that compound 1e exhibited significant analgesic activities using different processes, such as tail flick and writhing methods.

Similarly, Shiradkar and his co-workers reported the synthesis of N-{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amide derivatives using the microwave organic reaction enhancement method. The

synthesized compounds were further screened for antitubercular activity against the Mycobacterium TB H37 Rv strain using the Microplate Alamar Blue Assay MABA assay method. Some compounds, such as 3b, 3c, 5a, 5b and 5c, exhibited better antibacterial activities against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhosa*, and *Pseudomonas aeruginosa*, while compounds 5a, 5b and 5c exhibited better antitubercular activities against *M. tuberculosis* strain H37 Rv (Scheme 2).<sup>32</sup>

Virk *et al.* investigated the synthesis of N-substituted-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]propanamide derivative (7a-r) in which 1,2,4-triazole and piperidine rings were incorporated through microwave-assisted and conventional methods (Scheme 3). They reported that microwave-assisted synthesis was carried out in just 33–90 seconds with a remarkable 82% yield, while the conventional method required several hours to complete. The research group also evaluated the biological potential of these compounds against  $\alpha$ -glucosidase and acetylcholinesterase (AChE) enzymes. The methodology provides valuable insights into applications of microwave technology in organic synthesis for rapid and efficient compound production.<sup>33</sup>

Further, Shaikh *et al.* developed triazole-derived Schiff bases featuring pyrazole and triazole nuclei (8a-e) through microwave (MW) irradiation at temperatures of 70–75 °C using polyethylene glycol-400 as a solvent. This approach provides desired products in a short time frame of just 15–20 minutes with an excellent yield (Scheme 4). The resulting Schiff bases can act as pivotal precursors for the synthesis of various biologically active ligands and heterocyclic compounds, highlighting their significance in the development of valuable coordination compounds. This method enhances reaction efficiency and



Scheme 2 Synthesis of *N*-{4-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amide derivatives.<sup>32</sup>

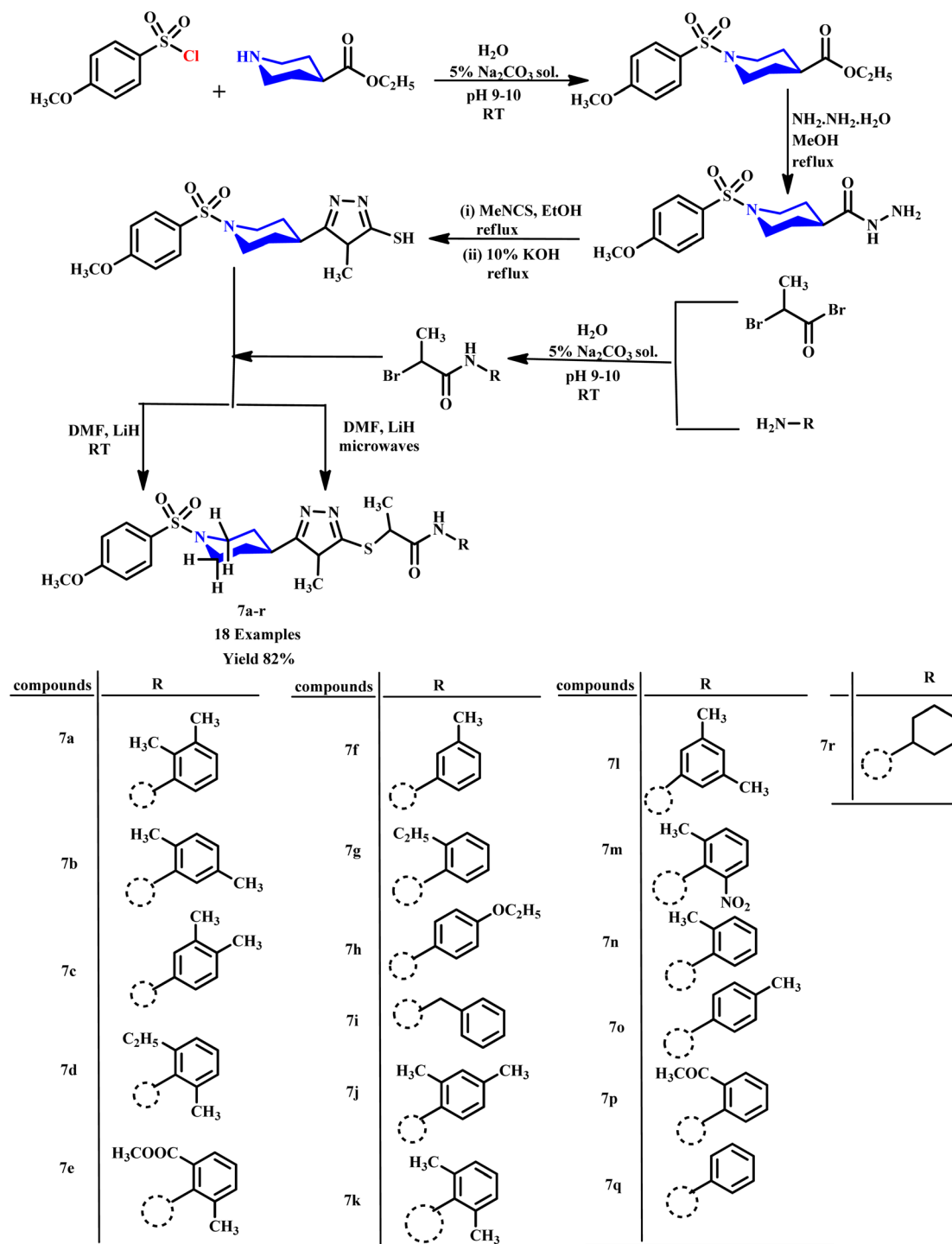
opens new avenues for research in medicinal chemistry and material science.<sup>34</sup>

In the progress of green protocol development for triazoles, Shcherbyna utilized a Milestone Flexi Wave Microwave system for the synthesis of novel series of 4-((5-((cyclohexylmethyl)thio)-4-*R*1-4*H*-1,2,4-triazol-3-yl)methyl)morpholines (**9a–e**) and 4-((4-*R*1-5-(pyridin-2-ylthio)-4*H*-1,2,4-triazol-3-yl)methyl)morpholines

(**10a–e**) as depicted in Scheme 5. The Milestone Flexi Wave Microwave system facilitates reaction completion in a minimum time (10.0 minutes) compared to the traditional method of heating.<sup>35</sup>

Similarly, Virk *et al.* synthesized *N*-(substituted)-5-((1-(4-methoxy phenylsulfonyl)piperidin-4-yl)-4*H*-1,2,4-triazol-3-ylthio) acetamide moieties (**11a–k**) using microwave-assisted



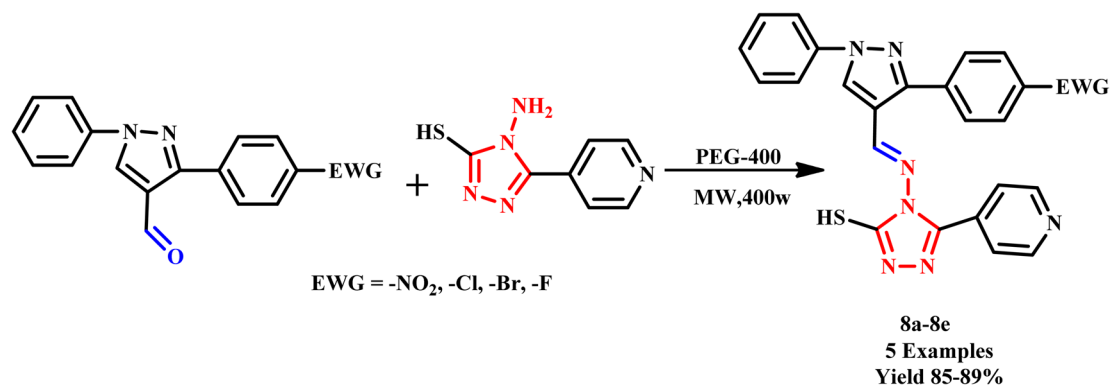


**Scheme 3** Synthetic route of *N*-substituted-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4H-1,2,4-triazol-3-yl)sulfonyl]propanamide derivatives (7a-r).<sup>33</sup>

methods. In this methodology, the reaction was completed within 31–68 seconds with extraordinary product yield, as shown in Scheme 6. The synthesized compounds were further examined owing to their inhibition potential against acetylcholinesterase (AChE), bovine carbonic anhydrase (bCA-II) and butyrylcholinesterase (BChE) enzymes. Notably, microwave-assisted synthesis significantly outperformed conventional

methods, which typically required 9–19 hours for product formation, while reported methodologies drastically reduced reaction times from 19 hours to just 31–68 seconds.<sup>36</sup>

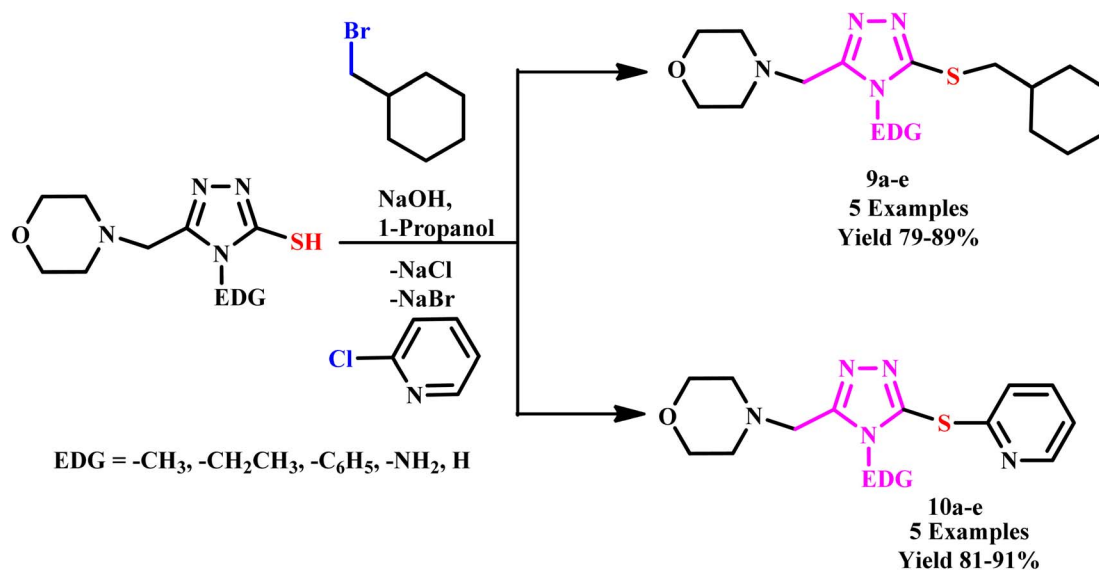
Piperazine-azole-fluoroquinolone-based 1,2,4-triazole derivatives were synthesized by Ozdemir *et al.* using an ethanol solvent under microwave irradiation with an impressive yield of 96%. This method significantly reduced the reaction time from



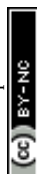
Scheme 4 Synthetic method for the synthesis of triazole-based Schiff bases (**8a-e**).<sup>34</sup>

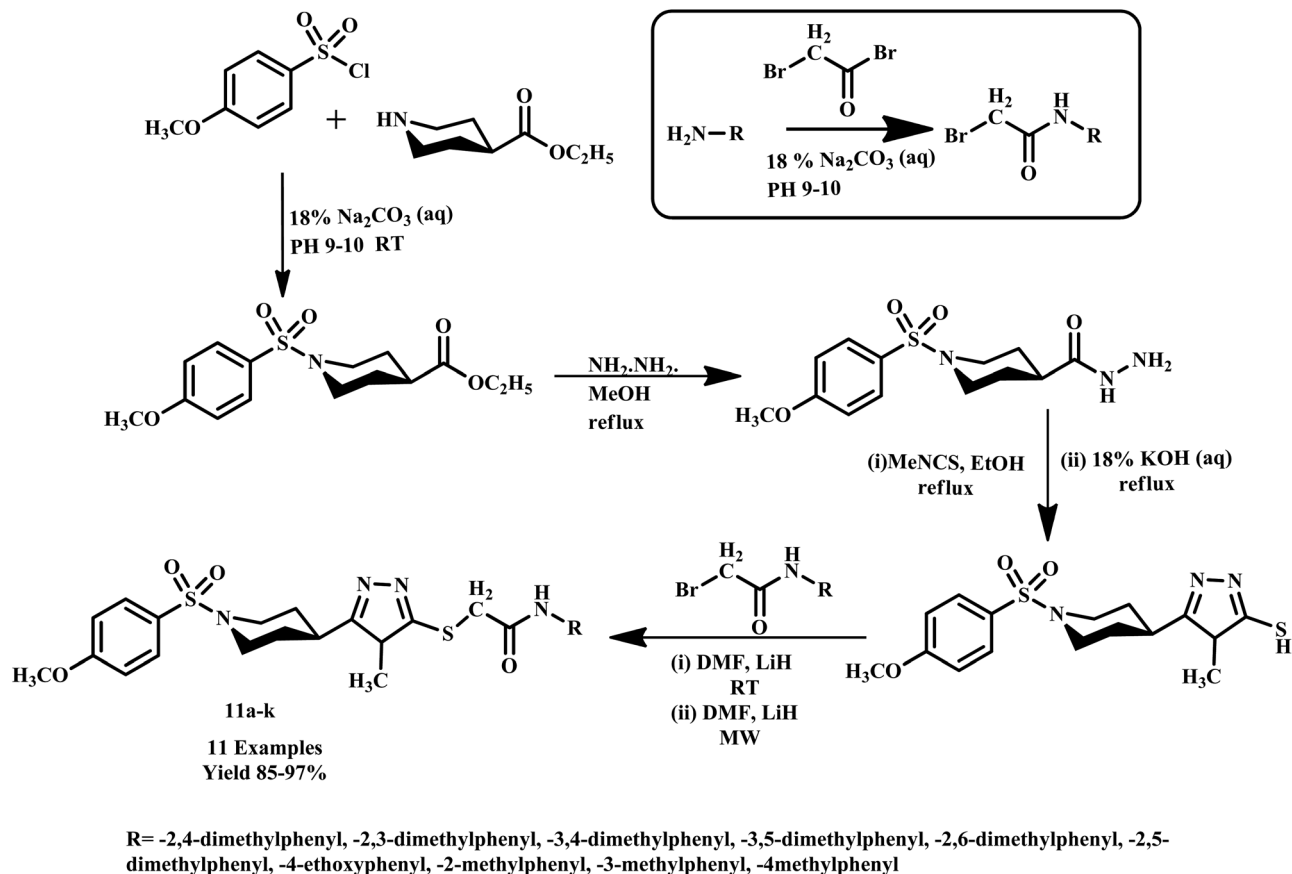
27 hours (under conventional heating) to just 30 minutes, highlighting the efficiency of microwave-assisted synthesis. The synthesized compounds were subsequently tested for antioxidant and antibacterial activities, which demonstrated good to moderate efficacy in both assays. These results demonstrate the potential of these derivatives as promising candidates for further pharmaceutical development.<sup>37</sup> In another study, Al-Soud and co-workers employed microwave irradiation for the synthesis of acyclic C-nucleosides, specifically 6-alkyl/aryl-3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles and their 6-arylthiomethyl analogues. This method reduced reaction time to 15–20 minutes at 120 °C, significantly accelerating the synthesis process. Among the synthesized compounds, 6-(3,4-dichlorophenyl)-3-(1,2-*O*-isopropylidene-*D*-ribo-tetritol-1-yl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole demonstrated notable antiviral activity against HIV-2.<sup>38</sup> Similarly, Cebeci and co-workers reported the synthesis of a novel hybrid combining 1,2,4-triazole with conazole and fluoroquinolone moieties under microwave irradiation within

a minimal time. They investigated the activity of these derivatives against various common infection strains. It was found that most of the reported compounds exhibited potent antibacterial activity against both Gram-positive and Gram-negative bacteria. Furthermore, certain derivatives have shown promising antiproliferative effects against HeLa cervical cancer cells and cytotoxicity towards normal cells.<sup>39</sup> In another report, ethyl 2-chloroacetate and 4-chlorophenol were utilized as starting materials for the synthesis of a novel series of thioether derivatives containing 1,2,4-triazole moieties (**12a-k**), as depicted in Scheme 7. The synthetic protocol developed by Min *et al.* employed microwave irradiation, resulting in an efficient reaction with an 81% yield within just 15 minutes. Additionally, several compounds from this series demonstrated notable antifungal activities, showcasing their potential as effective antifungal agents. This microwave-assisted synthesis of thioether derivatives containing 1,2,4-triazole moieties is an efficient and high-yielding method. Additionally, significant



Scheme 5 Synthesis of 4-((5-((cyclohexylmethyl)thio)-4-*R*1-4*H*-1,2,4-triazol-3-yl)methyl)morpholines and 4-((4-*R*1-5-(pyridin-2-ylthio)-4*H*-1,2,4-triazol-3-yl)methyl)morpholines (**9a-e** & **10a-e**).<sup>35</sup>



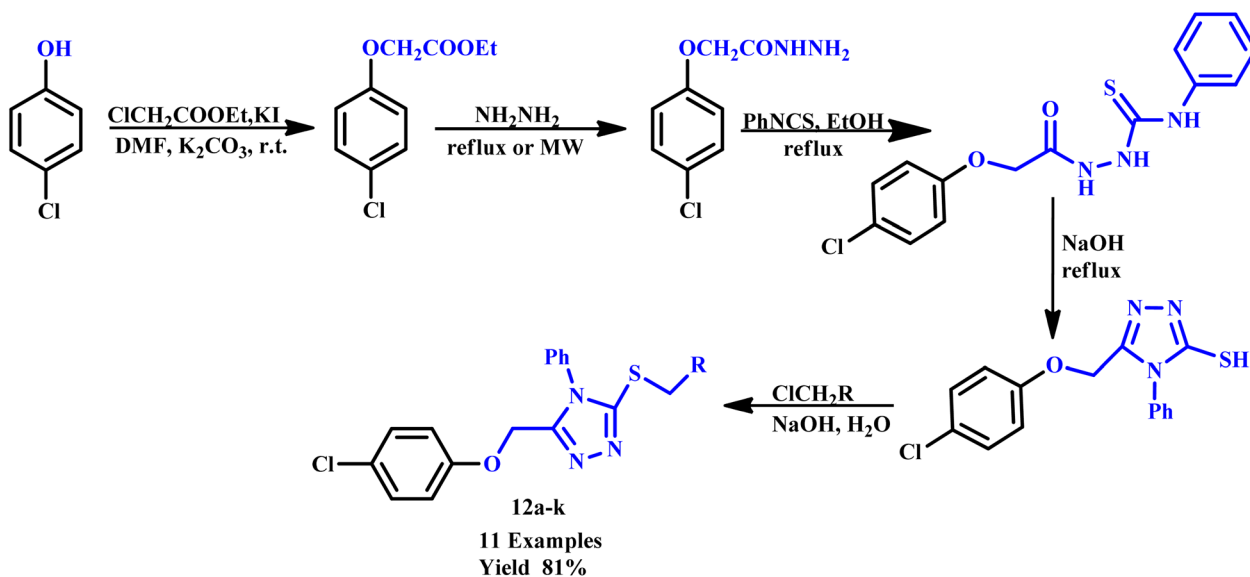


Scheme 6 Synthesis method of *N*-(substituted)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]acetamide (**11a-k**).<sup>36</sup>

antifungal activities highlight their potential for further development in pharmaceutical applications.<sup>40</sup>

In a subsequent report, Banerjee and co-workers developed Schiff base complexes of bis(cyclopentadienyl) titanium(IV) from

3-substituted-4-amino-5-hydrazino-1,2,4-triazoles using both conventional and microwave-assisted methods (Fig. 3). Under microwave irradiation, the reactions were completed within 10–15 minutes with good yields, while the conventional heating



Scheme 7 Synthetic route of thioether derivatives containing 1,2,4-triazole moieties (**12a-k**).<sup>40</sup>

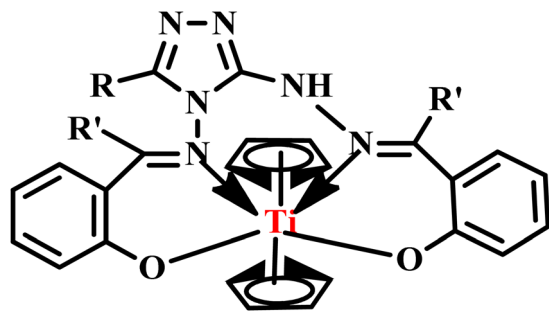


Fig. 3 Structure of Schiff base complex bis(cyclopentadienyl) titanium(IV).<sup>41</sup>

method required 6–7 hours. Remarkably, the microwave method saved time and enhanced the overall efficiency of the synthesis. Additionally, Schiff base complexes demonstrated moderate to good antibacterial activity against various bacterial strains, highlighting their potential for medical applications.<sup>41</sup>

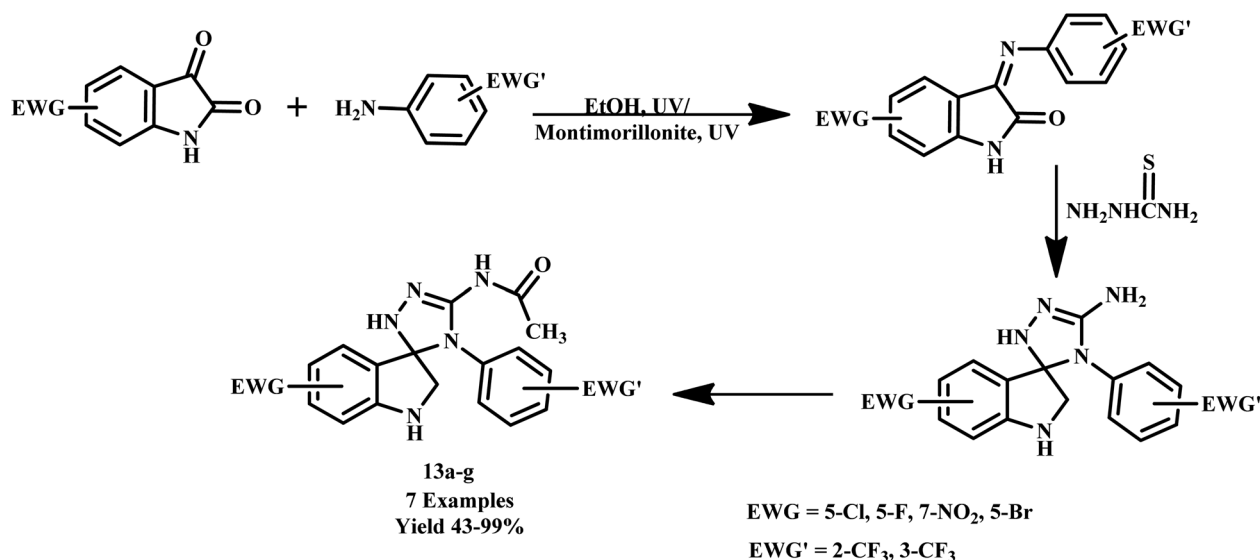
Franziska A. Brede synthesized transition metal complexes  $[\text{ZnCl}_2(\text{TzH})_2]$  and  $[\text{MCl}_2(\text{TzH})_4]$  (where  $\text{M} = \text{Mn}, \text{Fe}$ ;  $\text{TzH} = 1,2,4\text{-}H\text{-triazole}$ ) as precursors for the formation of coordination polymer ethers under microwave-assisted reactions. Remarkably, reported stiff chain-like coordination polymers and their precursor complexes exhibit significant differences in permittivity. In the synthesis, the utilization of microwave irradiation expedited the reaction process and resulted in a higher degree of polymerization. These findings highlight the potential of microwave-assisted synthesis in creating advanced materials with unique electrical properties.<sup>42</sup> Similarly, in another report, biologically active nalidixic acid-containing hybrid compounds were synthesized by Ceylan *et al.* through a microwave-assisted synthetic route. The reported compounds were produced with yields ranging from 43% to 99% within 5.0 minutes at 50 °C. This rapid and efficient synthesis highlights the significant potential of microwave-assisted techniques in streamlining the

production of complex pharmaceutical compounds. Further, Dandia *et al.* described a one-pot synthesis of a series of trifluoromethyl-substituted spiro[3*H*-indole-3,3'-[3*H*-1,2,4]triazole-2(1*H*)-ones (13a–g) via the condensation of thiosemicarbazide and 3-arylimino-2*H*-indole-2-ones under microwave irradiation with yields of 85–90%, as depicted in Scheme 8. This methodology not only offers greater selectivity and high purity but also significantly enhances the yield compared to conventional methods.<sup>43</sup>

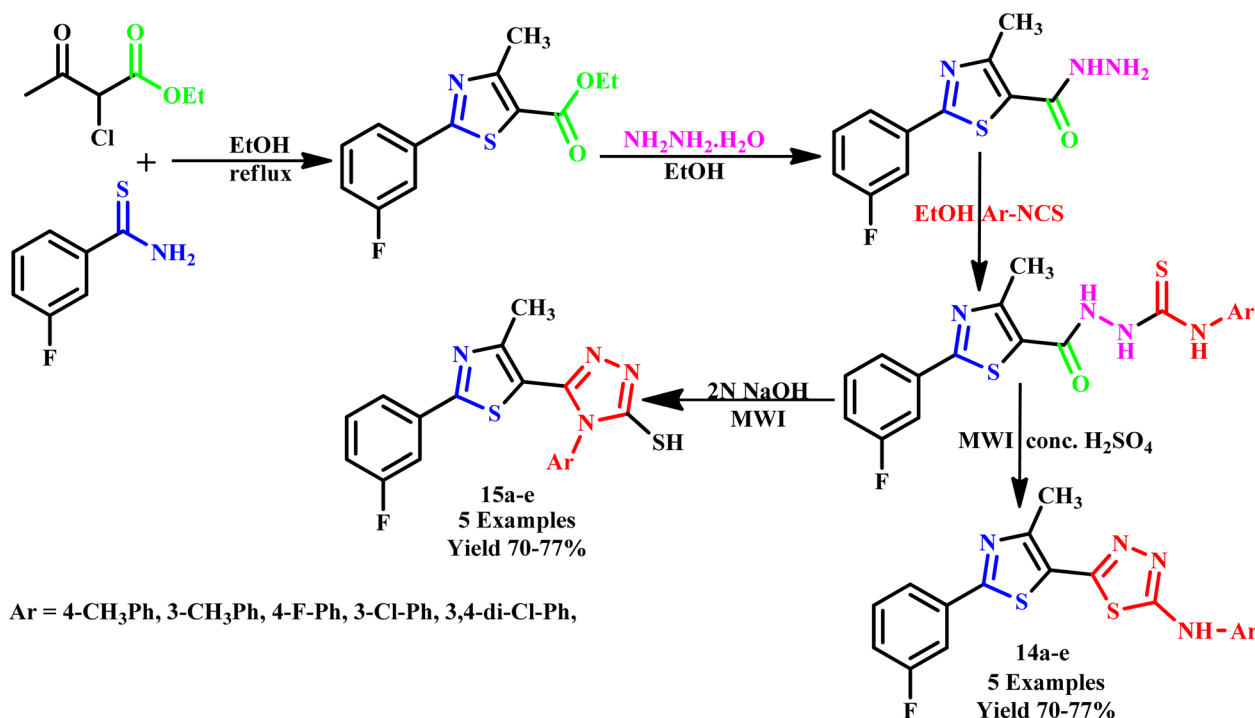
Similarly, Dengale and his coworker reported the synthesis of 5-[2-(3-fluorophenyl)-4-methylthiazol-5-yl]-*N*-phenyl-1,3,4-thiadiazol-2-amine (14a–e) and 5-[2-(3-fluorophenyl)-4-methylthiazol-5-yl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol (15a–e) from a 2-(3-fluorophenyl)-4-methylthiazole-5-carbohydrazide via cyclization under microwave irradiation with 77% yield, as depicted in Scheme 9. In this series of compounds, *N*-(3,4-dichlorophenyl)-2-[[2-(3-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]carbonyl]hydrazine carbothioamide and compound 15a showed better antibacterial activities against the *E. coli* strain. The reported compound 2-[[2-(3-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]carbonyl]-*N*-(3-methylphenyl)hydrazine carbothioamide (62.5  $\mu\text{g mL}^{-1}$ ) exhibited high activities against the *P. aeruginosa* strain. Compound 14c (250  $\mu\text{g mL}^{-1}$ ) and compound 15c (200  $\mu\text{g mL}^{-1}$ ) showed the highest activities against the *C. albicans* strain, and compound 14b (250  $\mu\text{g mL}^{-1}$ ) was examined to be highly active against *A. niger*.<sup>44</sup>

Later, in the progress of sustainable method development for triazoles, El Ashry *et al.* synthesized 4-amino-3-(*D*-gluco- and *D*-galacto-pentitol-1-yl)-5-mercapto-1,2,4-triazole (16a and 16b) via the condensation of thiocarbohydrazide and *D*-glucono- and *D*-galactono-1,5-lactone under a microwave-assisted protocol, as depicted in Scheme 10. The reaction yielded the product in an impressive 88% yield within just 5–6 minutes.<sup>45</sup>

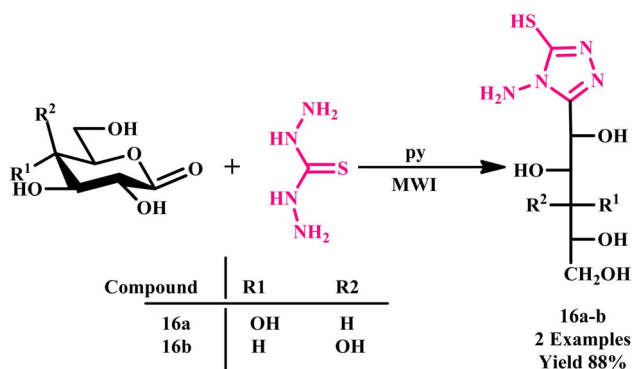
Further in a report, Jaisankar and his co-workers described easy and efficient microwave-assisted one-pot synthesis of 1,2,4-triazole-3-carboxamides derivatives (17a–h) using ester and



Scheme 8 Synthesis of tri fluoromethyl-substituted spiro[3*H*-indole-3,3'-[3*H*-1,2,4]triazole-2(1*H*)-ones (13a–g).<sup>43</sup>



Scheme 9 . Synthetic route of {5-[2-(3-fluorophenyl)-4-methylthiazol-5-yl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol or 5-[2-(3-fluorophenyl)-4-methylthiazol-5-yl]-*N*-phenyl-1,3,4-thiadiazol-2-amine} [14a–e and 15a–e].<sup>44</sup>



Scheme 10 Microwave-assisted synthetic protocol for 4-amino 3-(D-glucosyl)- and D-galacto-pentitol-1-yl)-5-mercapto-1,2,4-triazole (16a and 16b).<sup>45</sup>

amine in toluene under neutral conditions. The outcomes of this protocol were compared with conventional methods, revealing that the microwave-assisted reaction proceeded without the need for any catalyst and achieved high yields within just 30 minutes. In contrast, the same product formation takes approximately 12–16 hours using conventional methods (Scheme 11). This remarkable reduction in reaction time, along with the elimination of catalysts, underscores the significant advantages of microwave-assisted sustainable synthesis.<sup>46</sup>

A microwave-assisted synthesis of 3,5-dibenzyl-4-amino-1,2,4-triazole (18) was efficiently conducted in just 8–9 minutes at 250 W utilizing coupling of 2,4-pentanedione and diazotization reported by Jha and her co-workers (Scheme 12).

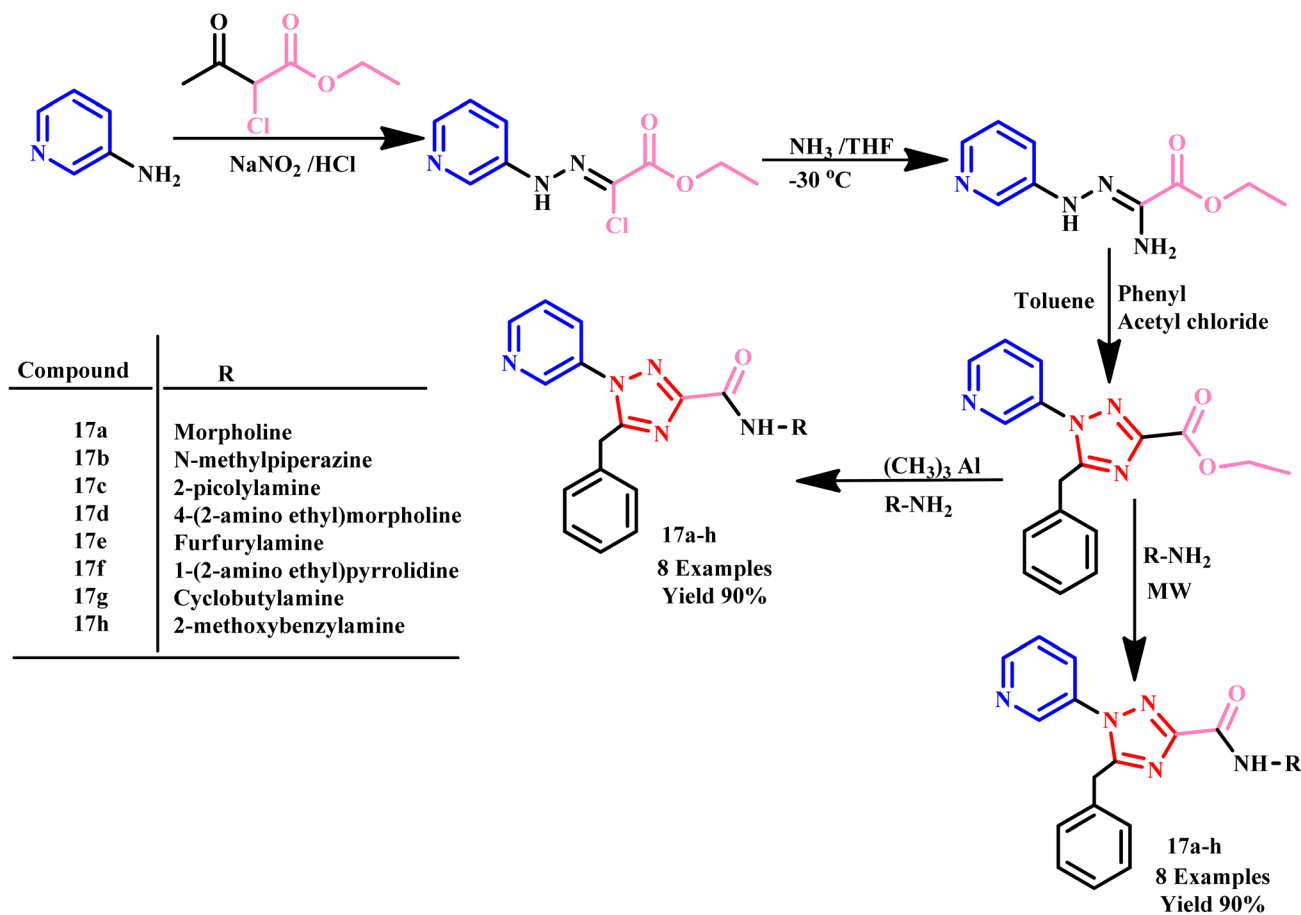
In contrast, the traditional method required a lengthy reflux time of 10 hours with equal ratios of reactants, highlighting the significant time-saving advantage of the microwave approach. Moreover, the study involved the formation of metal complexes screened for anticancer activity. Spectral analyses revealed that these metal complexes exhibited octahedral geometry. Notably, owing to the steric hindrance posed by large benzyl groups, only mononuclear complexes were successfully formed. The reported innovative methodology enhances synthesis efficiency and contributes to the development of potential therapeutic agents against cancer.<sup>47</sup>

Similarly, Kahveci *et al.* developed a microwave-assisted green synthetic protocol for the rapid synthesis of 3-aryl-4-arylmethylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives (19a–p). It was observed that utilization of microwave irradiation, reported compounds were formed in just 5.0 minutes with an impressive yield of 96%, as illustrated in Scheme 13. The synthesized derivatives demonstrated significant mycostatic activity against various *Candida* species, highlighting their potential application in antifungal therapy.<sup>48</sup>

The novel zinc(II) phthalocyanines and phthalonitrile containing pharmacologically active molecules, such as triazole and morpholine, were synthesized through microwave irradiation and the classical method by Kantar and his co-workers. The reported microwave approach was a viable alternative process and an appealing practical method for the synthesis of phthalocyanines, including morpholino-substituted triazole derivatives, due to outstanding product yields (92%), simple workup procedure and quick reaction time, as depicted in Scheme 14. It was found that under the microwave, the reaction was carried





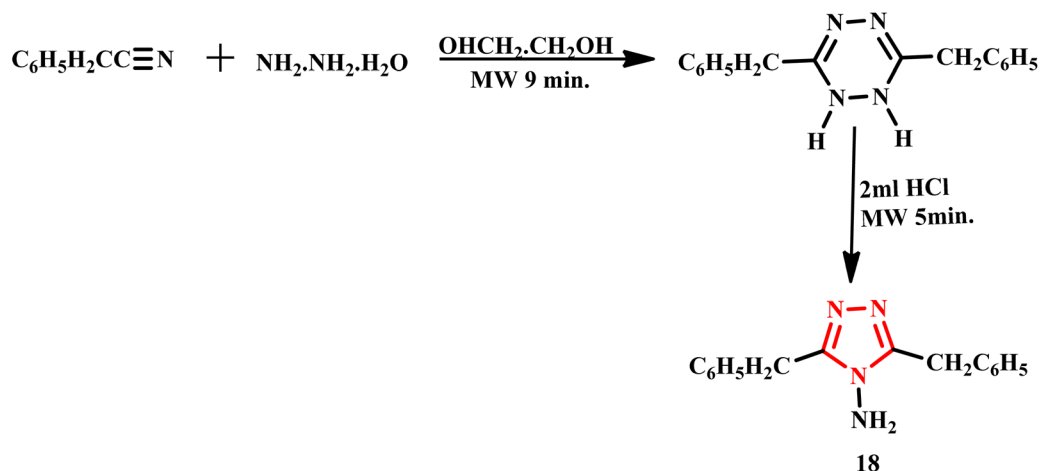


Scheme 11 Microwave-assisted synthesis of 1,2,4-triazole-3-carboxamide derivatives (17a–h).<sup>46</sup>

out within 10–13 minutes, while the same product formation took approximately 48.0 hours with 64–80% yield in the conventional method. The compound 4-[4-(3-morpholino-propyl)-5-phenyl-2H-1,2,4-triazol-3-one-1-yl] phthalonitrile exhibited promising anti-xanthine oxidase (anti-XO) inhibition with an  $IC_{50}$  value of  $0.082 \pm 0.004$  mM. The authors also

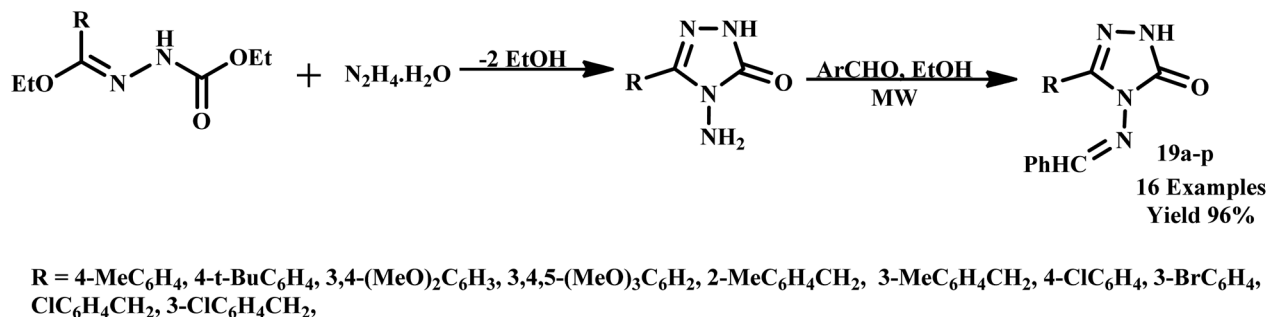
reported that the low solubility and high aggregation tendency of phthalocyanine compounds did not exhibit xanthine oxidase (XO) inhibition.<sup>49</sup>

Furthermore, Kidwai *et al.* synthesized 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepine derivatives (22a–e and 23a–e) using microwave irradiation. The reaction involved 1-amino-2-mercapto-5-



Scheme 12 Microwave-assisted synthetic protocol for 3,5-dibenzyl-4-amino-1,2,4-triazole (18).<sup>47</sup>





Scheme 13 Synthetic route of 3-aryl-4-arylmethylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-ones (**19a–p**).<sup>48</sup>

substituted triazoles and substituted chalcones and was completed within an impressive 60–120 seconds, as shown in Scheme 15. In contrast, the conventional heating method required a lengthy duration of 10–18 hours. This significant reduction in reaction time demonstrates the efficiency of microwave-assisted synthesis and offers a valuable approach for the rapid development of complex organic compounds.<sup>50</sup>

Similarly, in the progress of green microwave-assisted protocol developments, Kumar *et al.* developed one pot protocol for the synthesis of 3-phenyl-2-[4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl] thiazolidin-4-ones derivative from substituted phenyl azide, propargyl oxy-benzaldehyde, thio-glycolic acid and substituted aniline using of Cu(I)-catalyzed microwave-assisted synthesis.<sup>51</sup> Further, an efficient, easy and mild microwave-assisted method was developed by Shelkea and his coworker for the synthesis of substituted 1,2,4-triazoles derivative (**24a–q**) using formamide and hydrazines (Scheme 16). The MW-assisted protocol offered certain benefits, such as excellent yields, catalyst free conditions and short reaction time (in minutes) compared to the conventional method.<sup>52</sup>

Lee *et al.* developed a microwave-assisted facile and efficient one pot synthetic method for 1,3,5-trisubstituted-1,2,4-triazoles (**25a–f**) synthesis *via* cyclization with hydrazines, followed by an *N*-acylation reaction of amide derivatives. The reaction was completed within one minute with an 85% yield (Scheme 17) compared to the conventional method, which takes more than 4.0 hours.<sup>53</sup>

Further, microwave-assisted efficient and highly selective one pot synthetic method for 3,3'-(5,5')-polymethylene-bis(1H-1,2,4-triazol-5(3))-amines from the reaction of aminoguanidine and dicarboxylic acids in an aqueous medium was developed by Lim *et al.* The reaction was completed within 5.0 minutes at 200 °C under the MW method. This microwave-enabled one-pot approach yielded good yields and high purity of the desired products, demonstrating its scalability. The method's scope was effectively investigated by creating a small library of polymethylene-bis(1H-1,2,4-triazol-5(3))-amines with various alkyl chain linkers.<sup>54</sup> Similarly, Liu *et al.* developed some new fluorinated 1,2,4-triazole derivatives using the microwave irradiation method. Additionally, initial bioassays revealed that some of the compounds showed effective herbicidal properties. It was observed that when the reaction took place at room temp, it required more than 24.0 hours and obtained a low amount of

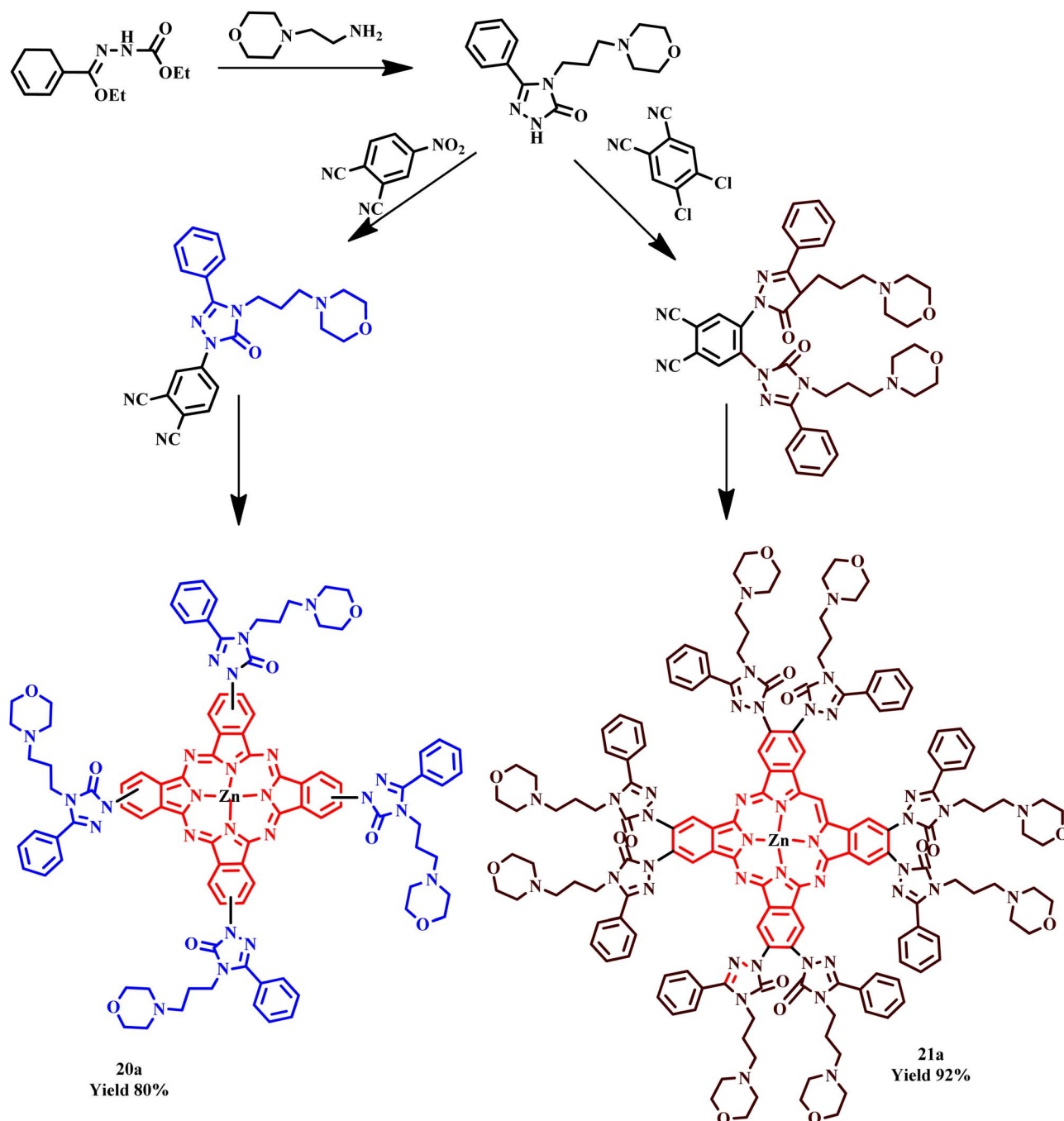
yield <5%, but under MW conditions, the reaction time interval from hours to few minutes (10.0 minutes) with a good amount of yield (56%). It was found that most of the reported compounds inhibited the growth of *B. campestris* (efficacy 66–89%), while all compounds showed low activities against *E. crusgalli*.<sup>55</sup> A robust regioselective microwave-assisted synthetic protocol for the synthesis of *N*-substituted 1,2,4-triazoles derivative (**26a–j**) was developed by Meng and Kung. This innovative approach involves the formation of several intermediates, evading target compounds through a cyclization reaction, as illustrated in Scheme 18. The advantages of this green protocol include high yields and minimal reaction times, making it an efficient choice for synthetic chemistry. The synthesized triazoles serve as valuable starting materials for subsequent alkylation or acylation reactions, enabling the production of trisubstituted triazoles with well-defined regioselective substitution patterns. This methodology not only streamlines the synthesis process but also enhances the potential for further functionalization in drug development and material science.<sup>56</sup>

Similarly, Meng *et al.* synthesized 1,2,4-triazole thioether derivatives in few minutes using the microwave-assisted methodology. The synthesized triazole derivatives exhibited moderate to good inhibition activity against *R. solani* and *C. orbiculare* at 50 µg mL<sup>-1</sup>.<sup>57</sup> Further, Sun and his co-worker synthesized a series of 1,2,3-thiadiazole rings containing 1,2,4-triazole derivatives (**27a–q**) under a multistep reaction through MW-assisted conditions (Scheme 19). According to the preliminary bioassays, some of the compounds displayed good fungicidal activities. It was observed that the best reaction conditions were 90 °C for 15 minutes under microwave irradiation.<sup>58</sup>

Further, Nas *et al.* synthesized metal-free 4-(2-(4-(4-methoxybenzylamino)-5-oxo-3-*p*-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)ethoxy) phthalonitrile and its complex with Ni(II), Zn(II), Co(II), Pb(II) and Cu(II) derivatives (**28a–f**) (Scheme 20).<sup>59</sup>

Nesaragi *et al.* developed a regioselective microwave-assisted synthesis of quinolin-3-yl-methyl-1,2,3-triazolyl-1,2,4-triazol-3(4H)-one derivatives (**29a–m**). This methodology was achieved through the [3 + 2] cycloaddition reaction of azides with terminal alkynes, resulting in impressive yields of 88–92%, as shown in Scheme 21. The reported efficient method highlights the versatility of microwave-assisted techniques and



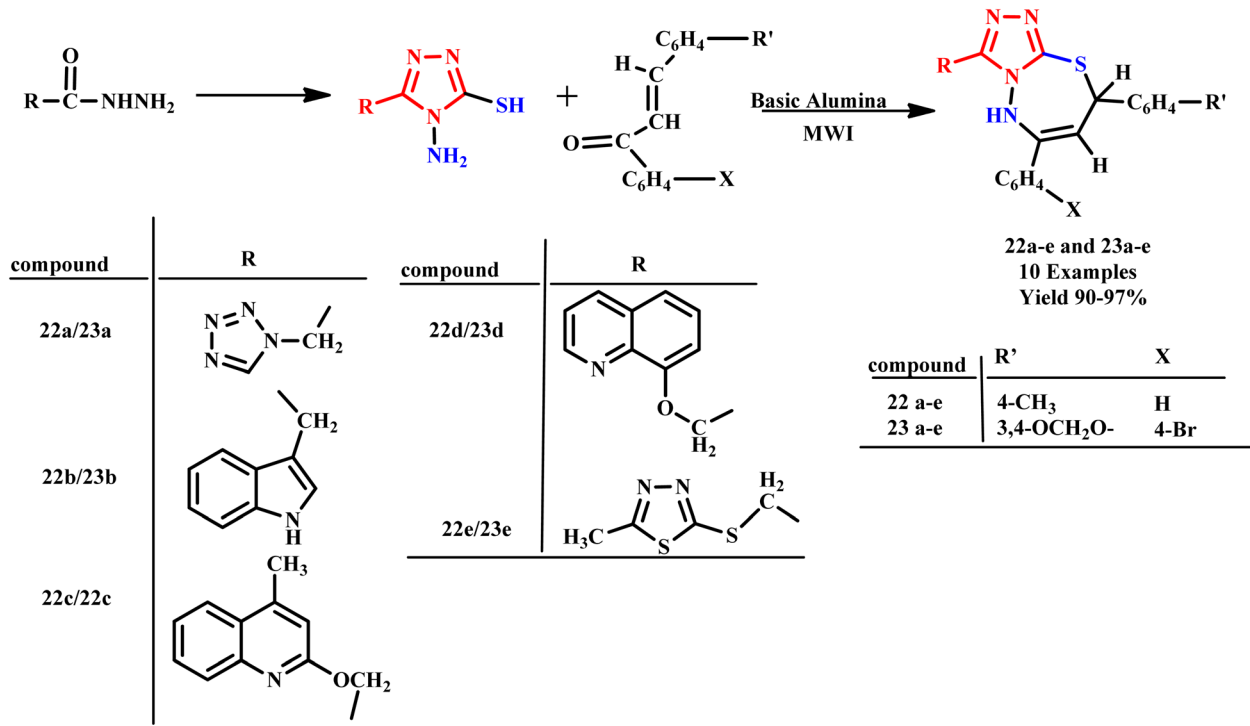


**Scheme 14** Synthetic route of 4-(3-morpholinopropyl)-5-phenyl-2*H*-1,2,4-triazol-3-one, 4-[4-(3-morpholinopropyl)-5-phenyl-2*H*-1,2,4-triazol-3-one-1-yl] phthalonitrile and 4,5-bis[4-(3-morpholinopropyl)-5-phenyl-2*H*-1,2,4-triazol-3-one-1-yl] phthalonitrile and zinc phthalocyanines (20a and 21a).<sup>49</sup>

demonstrates its potential for producing complex triazole derivatives with high regioselectivity.<sup>60</sup>

An efficient, fast and straightforward method was developed by Rahimizadeh *et al.* for one-pot synthesis of 6-aryl-3-substituted 5*H*-1,2,4-triazolo[4,3-*b*][1,2,4]triazoles. This synthesis involved the heterocyclization of the *N*-(3-methylthio-5-substituted-4*H*-1,2,4-triazol-4-yl)benzene carboximidamide derivative (30a-e) using microwave irradiation under solvent-free conditions. Compared to conventional heating methods,

microwave irradiation was 36–72 times faster and resulted in significantly higher yields, as illustrated in Scheme 22. It was found that the conventional heating methodology required 130 minutes to achieve a modest 25% yield, while the microwave method completed the reaction in just 10.0 minutes with an impressive yield of 77%. This advancement highlights the effectiveness of microwave-assisted synthesis in enhancing both efficiency and productivity in chemical reactions.<sup>61</sup>

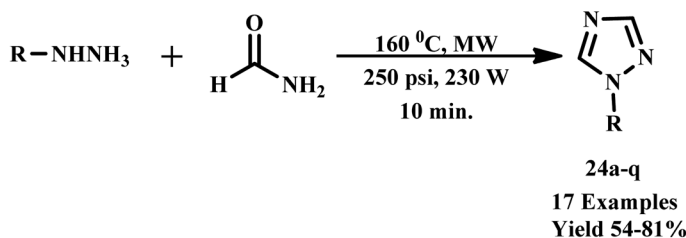
Scheme 15 Synthesis of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepine compounds (22a-e and 23a-e).<sup>50</sup>

Similarly, Aouad *et al.* reported a simultaneous inhibition study of CA II, VEGFR-2 and MMP-2 using 1,2,3- and 1,2,4-triazole hybrids that were carefully crafted using a pharmacophore hybridization technique and bearing diverse sulfonamide appendages. In the synthesis, a microwave-assisted click 1,3-dipolar cycloaddition process involving 4-azido benzene sulfonamides and different alkynes was used for the production of 1,2,4-triazole derivatives in a quantitative yield.<sup>62</sup> In another report, Wei *et al.* described a new and convenient *in situ* metal/ligand reaction for the synthesis of a series of 3,5-disubstituted-1,2,4-triazole derivative (31a-f) *via* the cycloaddition reaction of ammonia and organo-nitriles under the microwave-assisted condition with 85% yield within 1.5 hours. It was reported that a similar reaction was completed within 72 hours using a hydrothermal process (Scheme 23).<sup>63</sup> A comparative analysis

of microwave-assisted 1,2,4-triazole synthesis with conventional methods is presented in Table 1.

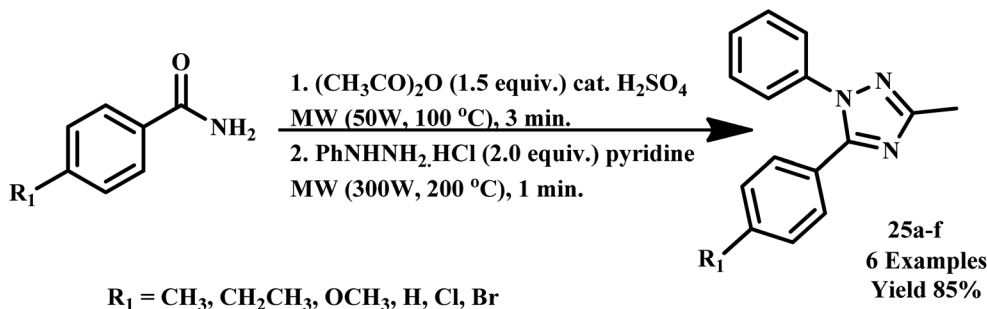
## Microwave-assisted synthesis of 1,2,3-triazole and derivatives

Another member of the triazole family, the 1,2,3-triazole ring, is another important heterocyclic scaffold that exhibits a wide range of applications in various domains. Owing to the wide range of applications, 1,2,3-triazoles with different substituents have drawn enormous attention for utilization in the fields of chemistry, medicine, and biology. For example, this scaffold is extensively explored in the development of anticonvulsant, antifungal, and notably well-liked anti-cancer medicines.<sup>64</sup> In this line, a convenient and simple method was reported by Subhashini *et al.* for the synthesis of a new series of imidazole



R = 4-MeOC<sub>6</sub>H<sub>4</sub>, 2-MeC<sub>6</sub>H<sub>4</sub>, 3-MeC<sub>6</sub>H<sub>4</sub>, 3,4-MeC<sub>6</sub>H<sub>3</sub>, 4-t-BuC<sub>6</sub>H<sub>4</sub>, t-Bu, C<sub>6</sub>H<sub>10</sub>, 3-FC<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 3-Cl-4-MeC<sub>6</sub>H<sub>5</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 4-NCC<sub>6</sub>H<sub>4</sub>

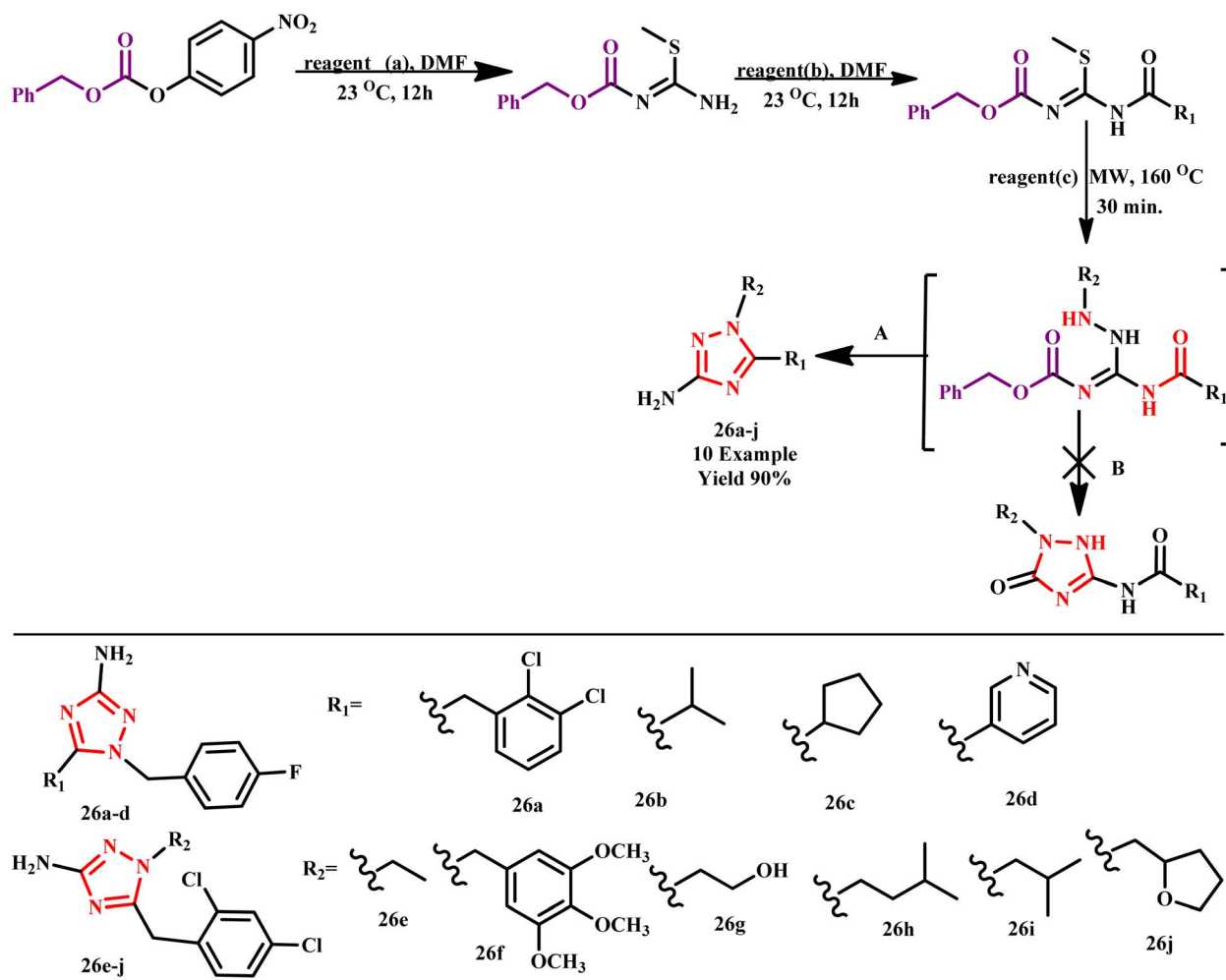
Scheme 16 Microwave-assisted 1,2,4-triazole synthesis using formamide and hydrazine (24a-q).<sup>52</sup>



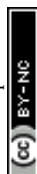
Scheme 17 Microwave-assisted synthetic protocol for 1,3,5-trisubstituted-1,2,4-triazole synthesis (25a–f).<sup>53</sup>

linked-1,2,3-triazole compounds (32a–h) through the MW method from 4-hydroxy benzaldehyde using click reaction within 3–5 minutes, as depicted in Scheme 24. It was observed by a research group that most of the synthesized hybrid compounds showed *in vitro* anti-microbial and antioxidant activity. In contrast, in conventional methods, the desired product was formed in 5.0 h at 80 °C. The antibacterial,

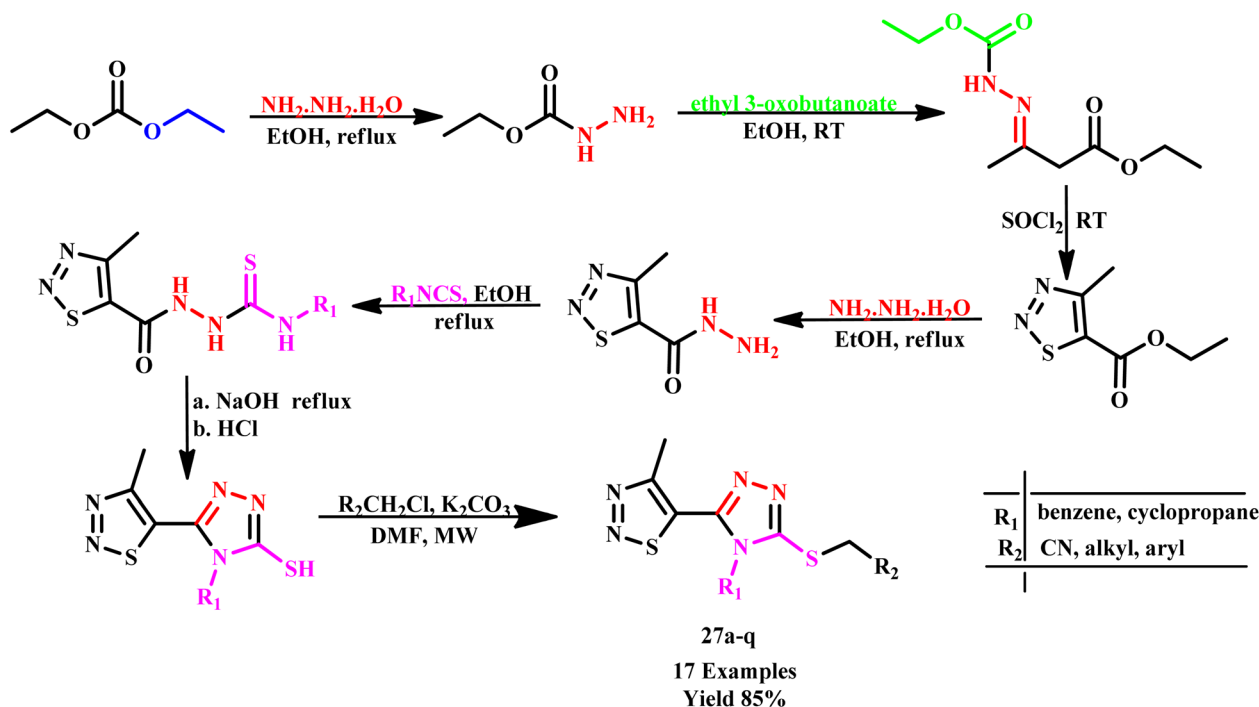
antioxidant and molecular docking properties of these compounds were investigated using the Schrodinger suite. Preliminary results showed that several target compounds showed potential antibacterial potency owing to their *in vitro* antimicrobial activity against Gram-positive and Gram-negative pathogens. Additionally, these compounds were examined using four distinct techniques for the *in vitro* antioxidant



Scheme 18 Microwave-assisted synthesis of *N*1-substituted 1,2,4-triazoles (26a–j). Condition: (a) 2-methyl-2-thiopseudourea sulfate; (b) carboxylic acid, 4-methylmorpholine, *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole; (c) substituted hydrazine, triethylamine.<sup>56</sup>







Scheme 19 Microwave-assisted synthesis of 1,2,3-thiadiazole rings containing 1,2,4-triazole derivatives (27a–q).<sup>58</sup>

activity. A small number of them showed excellent antioxidant activity. Furthermore, *in silico* molecular docking experiments provided additional support for the activity relationship between these compounds.<sup>65</sup>

Similarly, Roshandel *et al.* reported solvent and catalyst-free microwave-assisted synthetic protocol for 1,2,3-triazole derivatives (33a–p) *via* cycloaddition reaction of acetylenes and trimethylsilylazide, as depicted in Scheme 25. In their synthetic method, diphenylacetylene was utilized as a model compound. By employing a thermally stable azide source and eliminating the need for solvents, metal catalysts, or other additives, the researchers were able to achieve the synthesis of 1,2,3-triazoles on a practical scale. This approach resulted in good to excellent yields (55–99%) and showcased a more environmentally friendly methodology that adheres to green chemistry principles while maintaining efficiency in triazole production.<sup>66</sup>

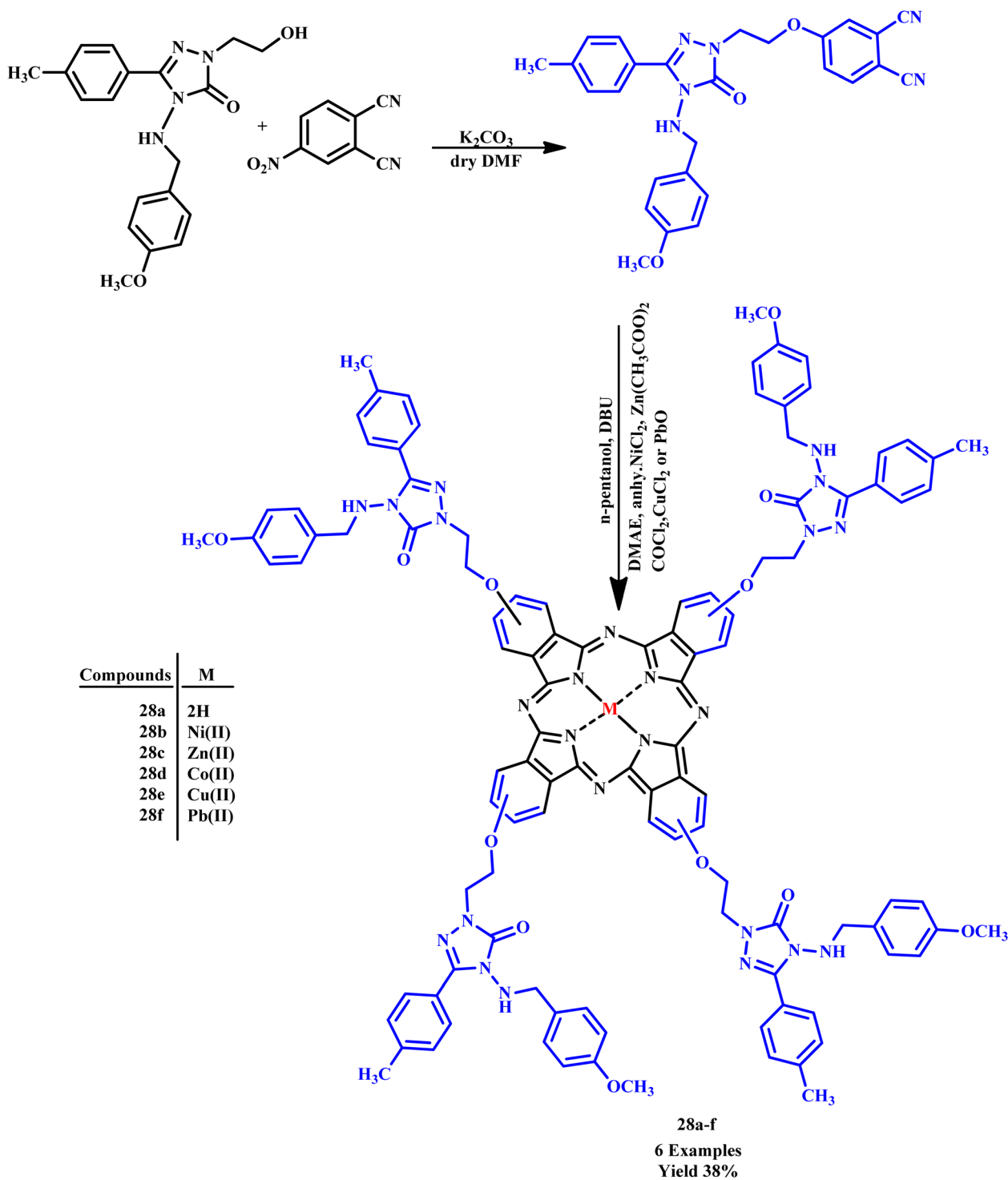
Further, in another report, an efficient microwave-assisted synthetic method was developed by Krim and his co-workers for the synthesis of 1,2,3-triazole and bis-1,2,3-triazole acyclonucleoside analogues of acyclovir. Remarkably, the reaction was completed in only 1.0 minutes with a yield of 93%, while conventional methodologies required three hours for completion. A series of novel nucleobase-linked 1,2,3-triazole acyclonucleosides were synthesized using copper(i) as a catalyst to facilitate the 1,3-dipolar cycloaddition of *N*-1-propargylpyrimidines, *N*-1-propargylindazoles or *N*-9-propargylpurine with azido-pseudo sugars under microwave conditions.<sup>67</sup> Further, in a report, Singh synthesized a series of triazole organo-silanes and triazole functionalized alkynes (34a–e) through microwave protocol. Surprisingly, microwave protocol offers a great alternative with 86–98% yield within 21.0 minutes, which is almost

sixteen times lower than conventional techniques (Scheme 26). Another research group reported that synthesized tris-triazole compounds exhibited high effectiveness for anti-parasitic and antioxidant treatment. Tris-triazole silane compound *Giardia lamblia* (Z)-*N*-(2,4-bis((1-(3-(triethoxysilyl) propyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzylidene)-4*H*-1,2,4-triazol-4-amine was determined to be the most effective treatment against *Trichomonas vaginalis*. This low-cost, multipurpose medication is hopefully useful in the eradication of parasitic diseases from the human population.<sup>68</sup>

Ashok and his co-workers reported a microwave-assisted synthetic protocol for a series of 3-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes and their benzimidazole derivatives (35a–g) with an 89% yield (Scheme 27). Among the synthesized compounds, 3-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde was proven to be a more effective antiproliferative agent for C6 cell, while 2-(3-(1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-yl)-1*H*-benzo [*d*]imidazole compound was proven to be a more effective antiproliferative agent for MCF-7 cell line. In conventional heating methodology, the reported reaction time required more than 6 hours to complete at room temperature with 66% yield, while it required 6–10 min at 300 W under MW irradiation conditions.<sup>69</sup>

Narsimha *et al.* reported a one-pot, copper-catalyzed synthesis of fused benzothiazino[1,2,3]triazolo[4,5-*c*]quinolinone derivatives (36a–f) and (37a–i) from 1-iodoalkynes and various aryl azides *via* intramolecular C–H arylation of the *in situ* generated 5-iodotriazole intermediate, as illustrated in Scheme 28. This innovative method showcases the efficiency of copper catalysis in complex organic syntheses. Notably, some of



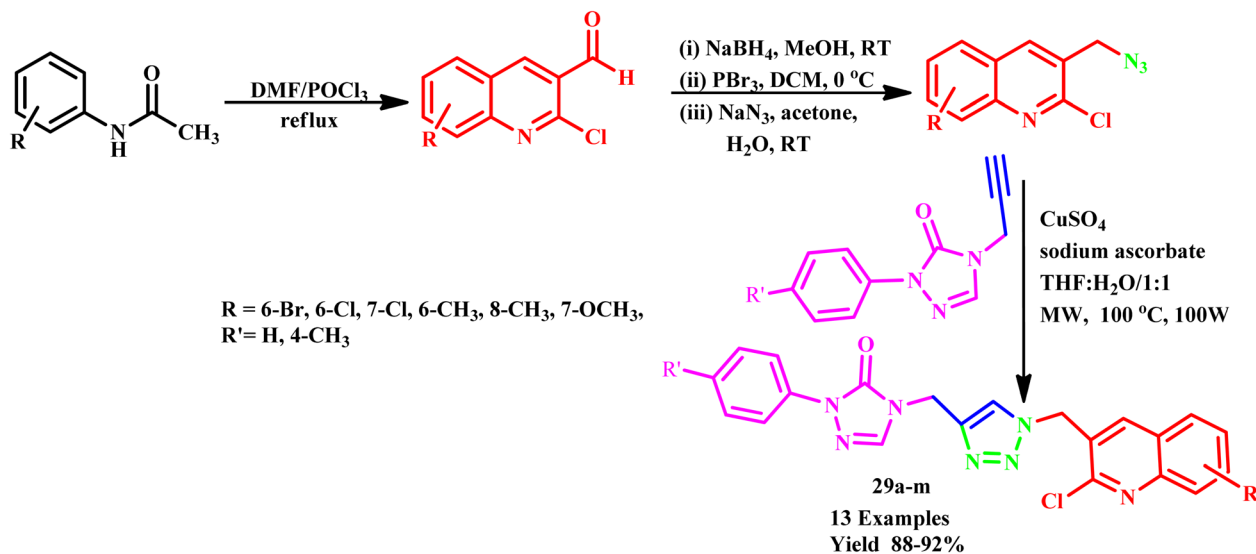


Scheme 20 Synthetic method for the synthesis of metallophthalocyanine and metal-free phthalocyanine (28a–f).<sup>59</sup>

the synthesized compounds demonstrated significant anti-cancer activities against the A-549 and MCF-7 cancer cell lines. In particular, compounds **37b** and **37c** exhibited high activity against both the A-549 and MCF-7 cell lines. These findings suggest that such compounds could be promising candidates for further development as anticancer agents.<sup>70</sup>

Further, a novel series of acridone-based 1,2,3-triazole hybrid derivatives (**38a–h**) were synthesized *via* copper(i)-catalyzed azide–alkyne cycloaddition (CuAAC) by Aarjane and his coworker within 10.0 minutes through the MW-assisted method with 69–86% yields (Scheme 29). The traditional methodology required at least 10.0 hours to complete the reaction, and overall yield was found to be in a range of 60–75%, while under



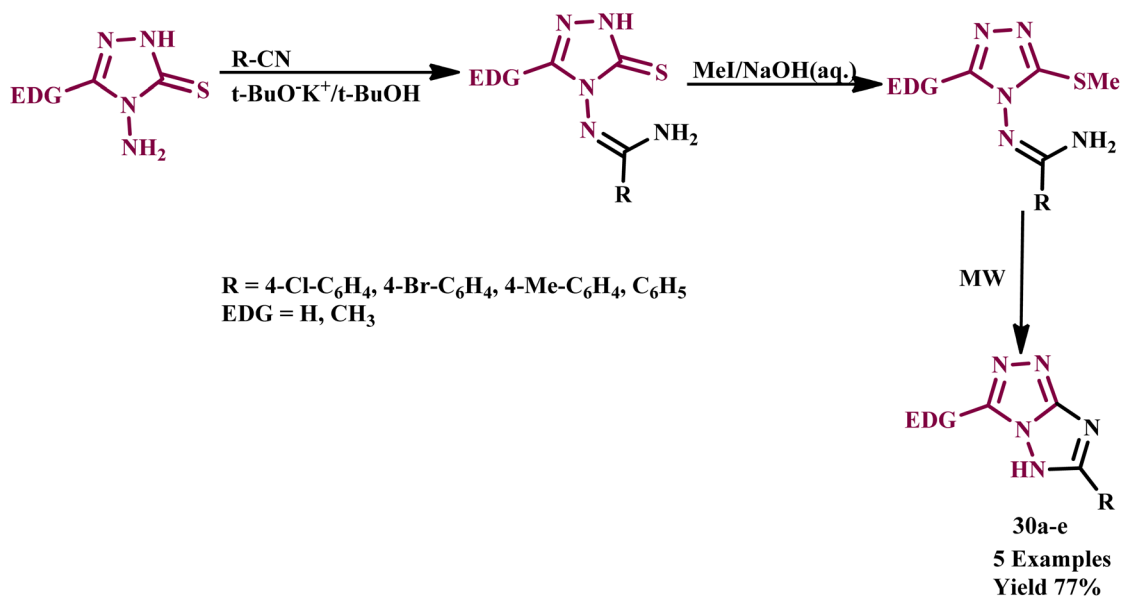


Scheme 21 Synthetic route of quinolinyl-1,2,3-triazolyl-1,2,4-triazol-3(4H)-one derivatives (29a-m).<sup>60</sup>

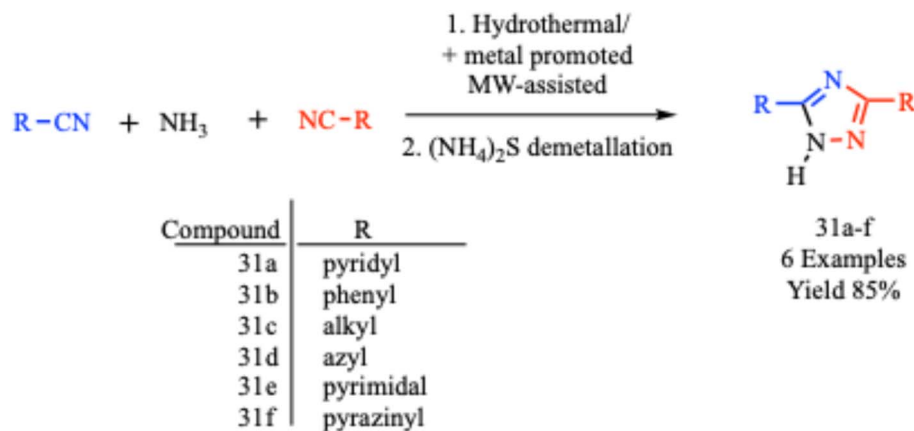
microwave-assisted reaction, product yield was improved, and reaction time was also reduced to few minutes. The structures of the acridon-1,2,3-triazole hybrid derivatives were identified using FTIR, NMR, and mass spectrometry. The synthesized derivatives exhibit antibacterial activity against *S. aureus*, *Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas putida*, and *Serratia marcescens*, indicating that the substitution of the acridone ring by the 1,2,3-triazole nucleus enhances the antibacterial potential of the compounds. Compound **38f** shows an excellent antibacterial effect against *S. aureus*.<sup>71</sup>

Similarly, a series of novel 1-(5-methyl-aryl-1H-1,2,3-triazol-4-yl)ethanone O-((1-aryl-1H-1,2,3-triazol-4-yl)methyl) oxime derivatives (**39a-p**) was prepared through Cu(I)-catalyzed 1,3-

dipolar cycloaddition of organic azides and alkynes under microwave irradiation (Scheme 30) by Ashok and his coworker. The O-alkoxy oxime linkage was used in this methodology to connect the two triazole moieties. Furthermore, some of these compounds showed good anti-fungal and antibacterial activities against the tested microorganisms. To obtain the desired product via the conventional method, the reaction was heated at 80 °C for 8 hours and produced 52% yield, while the MW method required 180 W for 12 minutes with 92% yield. Furthermore, synthesized compounds **39g** and **39i** showed excellent anti-fungal activities and compounds **39g**, **39i**, **39l** and **39h** showed excellent anti-bacterial activities against the tested microorganism.<sup>9</sup>



Scheme 22 Synthesis of N-(3-methylthio-5-substituted-4H-1,2,4-triazol-4-yl)benzene carboximidamides (30a-e).<sup>61</sup>



Scheme 23 Synthetic route for 3,5-disubstituted-1,2,4-triazole derivatives (31a–f).<sup>63</sup>

Du and team developed a highly efficient, rapid and facile microwave-assisted one-pot synthesis of 1-monosubstituted 1,2,3-triazoles (**40a–n**). This method utilized commercially available arylboronic acids, 3-butyne-2-ol and sodium azide, and achieved excellent yields within just 15.0 minutes at 80 °C (Scheme 31). In contrast, conventional methods require significantly longer reaction times to produce the target products. This innovative approach speeds up the synthesis process and enhances overall efficiency, which makes it a valuable advancement in the field of organic chemistry.<sup>72</sup>

A new series of *p*-toloxyquinoline-triazole hybrid derivatives (**41a**, **42a**, **43a–41d**, **42d**, and **43d**) were prepared by Vishnuvardhan and his coworker under microwave irradiation from hydroxylacetophenes and 2-(*p*-toloxy)quinoline-3-carbaldehyde, as depicted in Scheme 32. It was observed that in the microwave method, the reaction was completed within 5–6 min with 93% yield, and in the conventional method, the reaction required more than 8–10 hours to complete with 75% yield. The desired 1,2,3-triazole compounds were produced through the 1,3-dipolar cycloaddition of alkynes with azides using CuI as a catalyst under a microwave-assisted process. All the reported compounds were examined with antimicrobial activities in which most of the compounds revealed the highest powerful zone of inhibition against all tested organisms. For example, some derivatives (**41d**, **42d** and **43c**) exhibited anti-fungal activities against *Candida metapsilosis* and *Aspergillus Niger* organisms using Griseofulvin as standard drug whereas some derivatives (**41d**, **42d** and **43a**) exhibited excellent anti-bacterial activities against *S. aureus*, *B. faecalis*, *B. faecalis*, *E. coli*, and *B. faecalis* using Ampicillin as standard drug.<sup>4</sup>

Similarly, Jaafar and his co-workers developed a regioselective synthesis of *N*-bis-1,2,3-triazolo-linked-1,5-benzodiazepin-2-ones (BZD) using various aliphatic/aromatic moieties through the microwave irradiation method for 6–12 minutes at 400 W with 67–92% yield as depicted in Scheme 33. All the synthesized compounds were evaluated for their anti-oxidant and antimicrobial activities. Compounds **44h** and **44k** showed anti-fungal activities. Furthermore, compounds **44g**

and **44h** exhibited anti-oxidant activities rather than other bis-triazole benzodiazepines.<sup>73</sup>

In another report, Dürüst and Karakuş reported simple microwave-assisted one pot synthesis of 1,2,4-oxadiazol-5-ylmethyl-1,2,3-triazoles derivatives (**45a–k**) through 1,3-dipolar cycloaddition of phenyl propiolic acid and azidomethyl 1,2,4-oxadiazoles, as depicted in Scheme 34. In this methodology, sodium-ascorbate and CuSO<sub>4</sub> are used as catalysts in ethanol/water solvent. The reaction mixture was then irradiated on the Cem Discover microwave reactor for 2.5 minutes at 0–80 W at 65 °C, with 75% yield, while the traditional method required 16.0 h to complete at 65 °C with 73% product yield. The benefits of the microwave-assisted method include slower reaction time, easy separation, simple work-up and reasonable yields.<sup>64</sup>

J. I. Sarmiento-Sánchez and co-workers reported the synthesis of 1,4-disubstituted 1,2,3-triazole derivatives (**46a–u**) via an *in situ* reaction of alkyl azides with various alkynes. They established that microwave irradiation significantly reduces reaction times from hours to minutes, which is an important advantage for the viability of novel synthetic techniques (Scheme 35). Furthermore, the yields of products obtained using microwave irradiation were higher than those achieved under standard thermal conditions. This advancement underscores the efficiency and practicality of microwave-assisted synthesis in organic chemistry.<sup>74</sup>

Similarly, a straightforward microwave-assisted methodology for the synthesis of novel 1,2,3-triazole compounds (**47a–h**) from acridone was developed by Aarjane *et al.* The typical synthesis includes regiospecific 1,3-dipolar cycloaddition between aromatic azides and 10-(prop-2-yn-1-yl)acridone derivatives using a Cu(I) catalyst (Scheme 36). In comparison to the traditional approach, microwave-assisted synthesis significantly shortened the reaction times and increased the yields of all reported compounds. It was observed that the microwave-assisted reaction was completed within 10.0 minutes at 200 W with 94% yield, while the conventional reaction required 4–8 h at 80 °C to complete with 62% yield. The FTIR, NMR, and mass spectrometry were used to determine the structures of the novel compounds.<sup>75</sup>



Table 1 Comparative analysis of microwave-assisted 1,2,4-triazole synthesis results with conventional methods

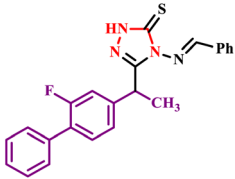
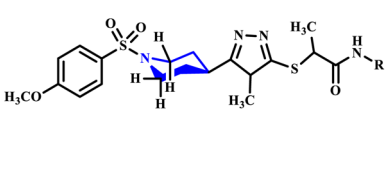
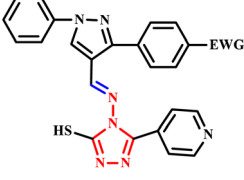
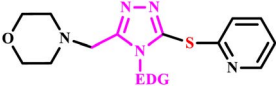
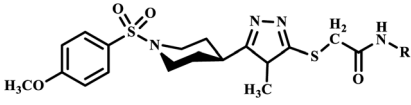
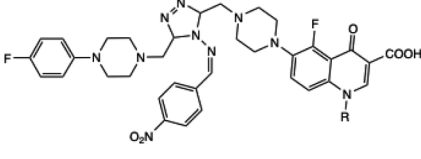
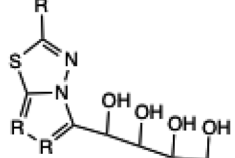
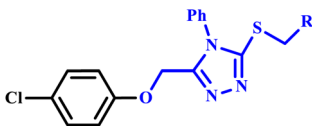
| Entry | Structure                                                                           | Name                                                                                                                                                                   | Conventional method |            |           | Microwave method |            |           | Ref. |
|-------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------|-----------|------------------|------------|-----------|------|
|       |                                                                                     |                                                                                                                                                                        | Time (hours)        | Temp. (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 1     |    | 4-(benzylideneamino)-3-(1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione derivatives                                                             | 3–5                 | 170–213    | 63–78     | 9–20             | 280–317    | 89–97     | 7    |
| 2     |    | <i>N</i> -{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amide derivatives                                                      | 0.5–0.75            | —          | 77        | 5–6              | —          | 77        | 32   |
| 3     |    | <i>N</i> -substituted-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4H-1,2,4-triazol-3-yl)sulfonyl]propanamide based on 1,2,4-triazole ring derivatives | 6–17                | RT         | 45–83     | 37–90 seconds    | —          | 82–97     | 33   |
| 4     |   | 4-((1,3-diphenyl-1H-pyrazol-4-yl)methyleneamino)-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiols                                                                           | —                   | —          | —         | 15–20            | 70–75      | 85–89     | 34   |
| 5     |  | 4-((5-((cyclohexylmethyl)thio)-4-R1-4H-1,2,4-triazol-3-yl)methyl)morpholines and 4-((4-R1-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)morpholines                | —                   | —          | —         | 10               | 160        | 79–81     | 35   |
| 6     |  | <i>N</i> -(substituted)-5-(1-(4-methoxyphenylsulfonyl)piperidin-4-yl)-4H-1,2,4-triazol-3-ylthio) acetamide derivatives                                                 | 9–19                | —          | 44–88     | 31–68 seconds    | —          | 85–97     | 36   |
| 7     |  | Piperazine-azole-fluoroquinolone based 1,2,4-triazole derivatives                                                                                                      | 27                  | —          | 91        | 30               | 125        | 96        | 37   |
| 8     |  | Acyclic (nucleosides of 3-(D-ribo-tetritol-1-yl)-5-mercapto-1,2,4-triazoles                                                                                            | 12                  | 80         | 73        | 15               | 120        | 87        | 38   |
| 9     |  | Thioethers containing 1,2,4-triazole derivatives                                                                                                                       | 24                  | RT – 90    | 78–42     | 15               | 90         | 81–87     | 40   |





Table 1 (Contd.)

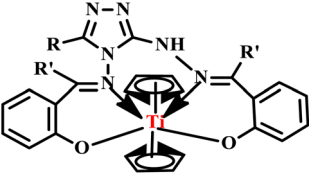
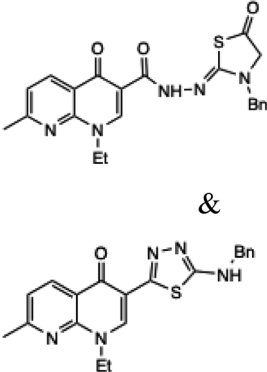
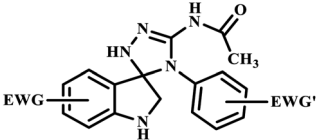
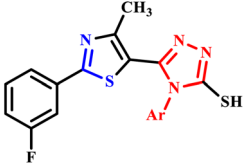
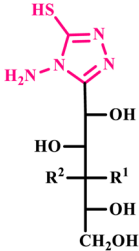
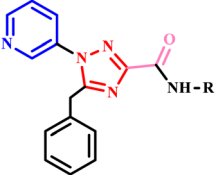
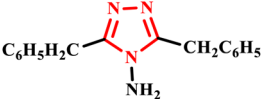
| Entry | Structure                                                                           | Name                                                                                                                                                                                                      | Conventional method |                             |           | Microwave method |            |           | Ref. |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------------------------|-----------|------------------|------------|-----------|------|
|       |                                                                                     |                                                                                                                                                                                                           | Time (hours)        | Temp. (°C)                  | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 10    |    | Schiff base complexes of bis(cyclopentadienyl) titanium(IV)                                                                                                                                               | 6–7                 |                             | 55–62     | 10–15            |            | 65–75     | 41   |
| 11    | —                                                                                   | Transition metal-based 1,2,4 triazole                                                                                                                                                                     | —                   | —                           | —         | 15               | 85–120     | —         | 42   |
| 12    |    | 3-(4-Benzyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one or 1-ethyl-3-(4-ethyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-7-methyl-1,8-naphthyridin-4(1H)-one | 14–16               | Ethanol/<br>water<br>reflux | 63–67     | 4                | 150        | 86–88     | 31   |
| 13    |   | Trifluoromethyl substituted spiro[3H-indole-3,3'-(3H-1,2,4-triazole)-2(1H)-ones                                                                                                                           | —                   | —                           | —         | 5–7              | 78         | 90–95     | 43   |
| 14    |  | 5-[2-(3-Fluorophenyl)-4-methylthiazol-5-yl]-4-phenyl-4H-1,2,4-triazole-3-thiol                                                                                                                            | 2–3                 | —                           | 60–69     | 5–8              | 350 W      | 70–77     | 44   |
| 15    |  | 3-(D-Alditol-1-yl)-4-amino-5-mercapto-1,2,4-triazole derivatives                                                                                                                                          | 1.5–2               | —                           | 70–80     | 5–6              | 201–217    | 80–88     | 45   |
| 16    |  | 1,2,4-Triazole-3-carboxamide derivatives                                                                                                                                                                  | 12–18               | 100                         | 60–80     | 30               | 130        | 65–90     | 46   |
| 17    |  | 3,5-Dibenzyl-4-amino-1,2,4-triazole                                                                                                                                                                       | 10–14               | Reflux                      |           | 8–9              | 250–300 W  | —         | 47   |



Table 1 (Contd.)

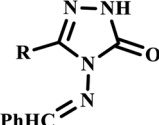
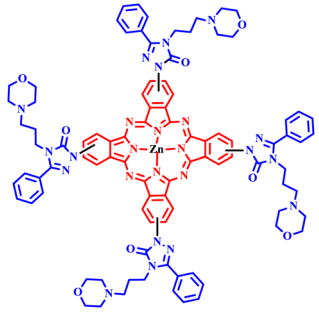
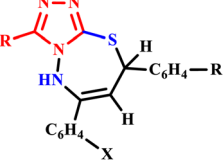
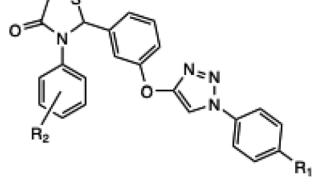
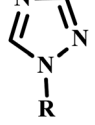
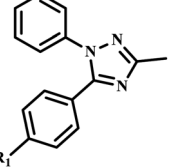
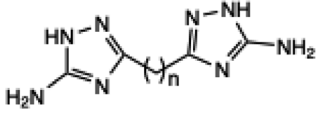
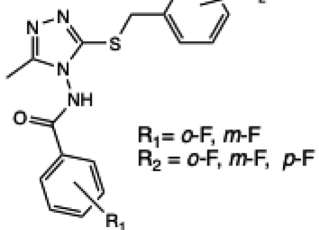
| Entry | Structure                                                                           | Name                                                                                                                   | Conventional method |            |           | Microwave method |            |           | Ref. |
|-------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|---------------------|------------|-----------|------------------|------------|-----------|------|
|       |                                                                                     |                                                                                                                        | Time (hours)        | Temp. (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 18    |    | 3-Aryl-4-arylmethylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one derivatives                                           |                     |            |           | 5                | 350 W      | 96        | 48   |
| 19    |    | Morpholino-substituted 1,2,4-triazole-3-one derivatives                                                                | 5                   | 150–155    | 30–64     | 13               | 125        | 70–92     | 49   |
| 20    |    | 1,2,4-Triazolo[3,4- <i>b</i> ]-1,3,4-thiadiazepine derivatives                                                         | 10–18               |            | 50–72     | 6–7              |            | 90–97     | 50   |
| 21    |   | 3-Phenyl-2-[4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl]thiazolidin-4-one derivative                             | —                   | —          | —         | 40–50            | 70         | 62–87     | 51   |
| 22    |  | Substituted 1,2,4-triazoles derivative                                                                                 | —                   | —          | —         | 10               | 160        | 54–81     | 52   |
| 23    |  | 1,3,5-Trisubstituted-1,2,4-triazoles derivative                                                                        | 4                   |            | 45–76     | 1.0              | 200        | 68–85     | 53   |
| 24    |  | Polymethylene-bis(1H-1,2,4-triazol-5(3)-amine) derivative                                                              | —                   | —          |           | 5                | 200        | 52–88     | 54   |
| 25    |  | Fluorinated 1,2,4-triazole derivatives<br>$R_1 = o\text{-F}, m\text{-F}$<br>$R_2 = o\text{-F}, m\text{-F}, p\text{-F}$ | —                   | —          | —         | 10               | 90         | 32–56     | 55   |

Table 1 (Contd.)

| Entry | Structure | Name                                                                       | Conventional method |            |           | Microwave method |            |           | Ref. |
|-------|-----------|----------------------------------------------------------------------------|---------------------|------------|-----------|------------------|------------|-----------|------|
|       |           |                                                                            | Time (hours)        | Temp. (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 26    |           | N1-substituted 3-amino-1,2,4-triazole derivative                           | —                   | —          | —         | 30               | 160        | 34–70     | 56   |
| 27    |           | 1,2,3-Thiadiazole rings containing 1,2,4-triazole derivatives              | 24                  | rt         | 78        | 15               | 90         | 85        | 58   |
| 28    |           | Metallophthalocyanine derivatives                                          | 24                  | 160        | 18        | —                | 175        | 38        | 59   |
| 29    |           | Quinolin-3-yl-methyl-1,2,3-triazolyl-1,2,4-triazol-3(4H)-ones              | 4–6                 |            | 74–80     | 3–5              |            | 88–92     | 60   |
| 30    |           | 6-Aryl-3-substituted-5H-[1,2,4]-triazolo[4,3-b][1,2,4]-triazole derivative | 6                   | 110–130    | 15–25     | 5–10             | 700–1000 W | 55–77     | 61   |
| 31    |           | 3,5-Disubstituted-1,2,4-triazole derivative                                | 72                  | 120–170    | 13–25     | 1.5              | 120–170    | 72–85     | 63   |

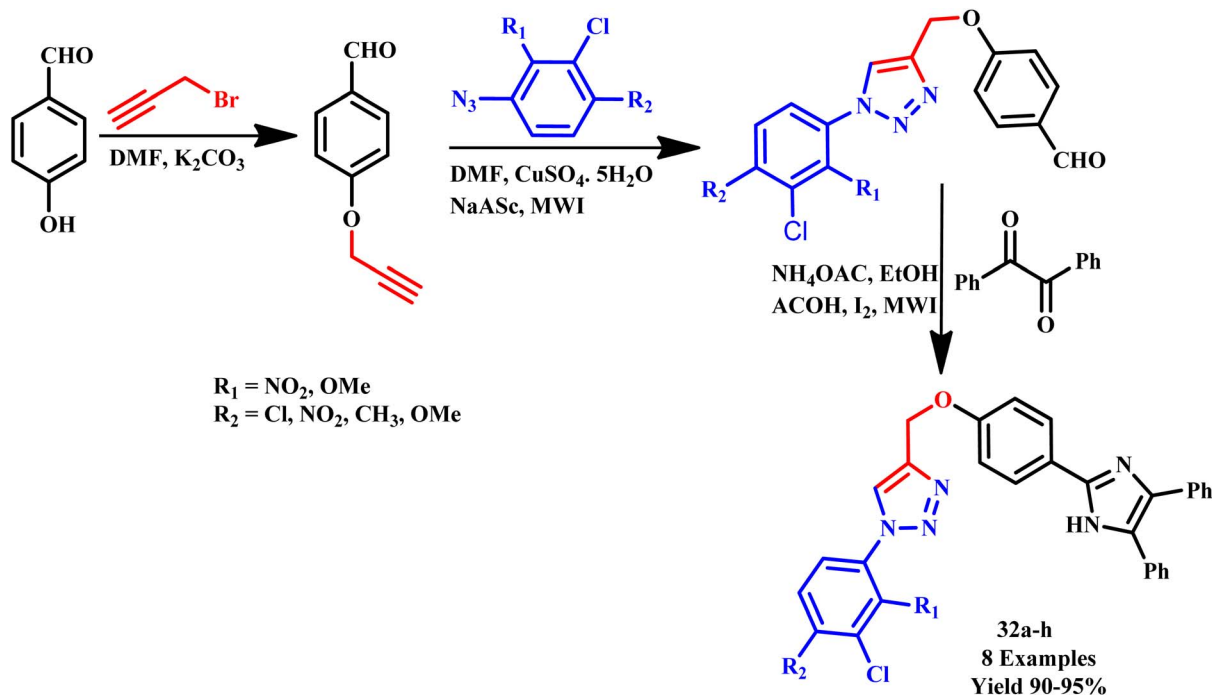
Further, a three-component reaction under microwave irradiation using allyl or benzyl halides, terminal alkynes, and sodium azide in the presence of neutral alumina-supported copper iodide was reported by Agalave *et al.* for 1,4-disubstituted 1,2,3-triazole derivative (**48a–s**) synthesis, as shown in Scheme 37. In this methodology, simple filtering was used to separate the products and catalyst and achieved a 98% yield of products in nearly pure form. It was found that the reaction was completed within 12.0 hours at room temperature, but in the microwave irradiation process (100 W, 78 °C), the reaction was completed within 6.0 minutes with 98% yield. This straightforward heterogeneous catalyst was reused for more than eight cycles while maintaining its high catalytic activities using water as a green solvent in a microwave process. Another environmentally friendly feature of this reaction was the ability to

isolate desired products in high yields through straightforward filtration without the need for column chromatography.<sup>76</sup>

In another study, Appukkuttan and his co-workers developed a microwave-assisted, regioselective, and efficient three-component protocol for the rapid synthesis of 1,4-disubstituted 1,2,3-triazole derivatives (**49a–m**) (Scheme 38). This approach enhances the effectiveness of the click chemistry process by making it more user friendly and safer by eliminating the need for organic azides by producing them *in situ*. In this methodology, the reaction time was drastically reduced from hours to just 10–15 minutes along with an improvement of yields (up to 90%).<sup>77</sup>

Similarly, an effective microwave-assisted synthesis of 1-[5-(1-benzyl-1H-[1,2,3]triazol-4-ylmethoxy)-2,2-dimethylchroman-6-yl]-3-aryl-propen-1-one and 1-[7-(1-benzyl-1H-[1,2,3]triazol-4-

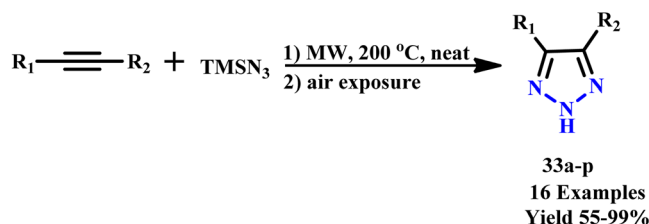


Scheme 24 Microwave-assisted synthetic protocol for 1,2,3 triazole derivatives (32a–h).<sup>65</sup>

ylmethoxy)-2,2-dimethyl-chroman-6-yl]-3-aryl-2-propen-1-ones was developed by Ashok and his coworker. They reported that CuI-catalyzed reaction required 24.0 h for completion and produced 72% yield, while microwave-assisted reaction required 8–10 h with 92% product yield. Most compounds were synthesized with ease of reaction conditions, such as smooth reaction conditions, purity and lower reaction times. Further, the *in vitro* antibacterial activity of all reported compounds was examined, and it was observed that phenyl ring containing compounds exhibited significantly higher antibacterial activity compared to other derivatives. Compound 1-[7-(1-benzyl-1*H*-[1,2,3]triazol-4-ylmethoxy-2,2-dimethyl-chroman-6-yl]-3-phenyl-propenone, 1-[7-(1-benzyl-1*H*-[1,2,3]triazol-4-ylmethoxy-2,2-dimethyl-chroman-6-yl]-3-(3,4-dimethoxy-phenyl)-propenone, 1-[7-(1-benzyl-1*H*-[1,2,3]triazol-4-ylmethoxy-2,2-dimethyl-chroman-6-yl]-3-(3,4,5-trimethoxy-phenyl)-propenone displayed maximum zone inhibition. All prepared compounds were screened *in vitro* for their antifungal activities against

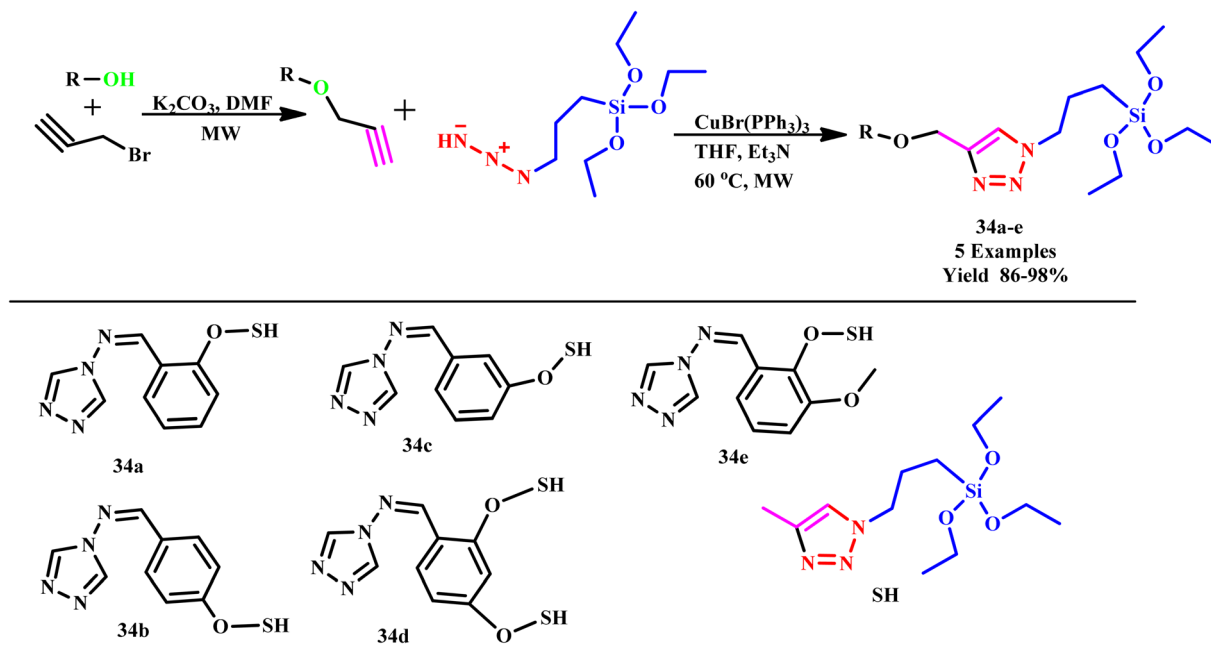
*Candida albicans* (ATCC-2091), *Aspergillus foetidus* (NCIM-505) and *Aspergillus niger* (ATCC9029).<sup>78</sup> Similarly, Ashok *et al.* synthesized bis-1,2,3-triazole derivatives based on 2-indolinone under microwave irradiation through copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) reaction of *O*-,*N*-propargylated indolinone derivatives (50a–t) with in situ-generated organic azides (Scheme 39). The conventional method gave a 70% yield at 80 °C for 7.0 hours, while the microwave-assisted synthetic protocol offered a 92% yield at 180 W within 3–5 minutes. Some derivatives, such as 50e, 50f and 50o exhibited outstanding radical scavenging activities compared with standard drugs BHT and ascorbic acid and showed promising antioxidant activities toward H<sub>2</sub>O<sub>2</sub>, NO radical and DPPH radical. Compounds 50g, 50h, 50n, 50q and 50r displayed excellent antimicrobial activities against fungal and bacterial strain.<sup>79</sup>

Ashok and his co-workers synthesized a series (51a–j) of biologically active dimers containing 1,2,3-triazole and



$R_1 = \text{-4-cynophenyl, -4-fluorophenyl, -4-chlorophenyl, -4-bromophenyl, -3,5-difluorophenyl, cyclopropane, -Phenyl, -ethylacetate, -naphthalene, -phenyl, -propane, -TMS}$   
 $R_2 = \text{H, ethylacetate, TMS, C}_2\text{H}_5$

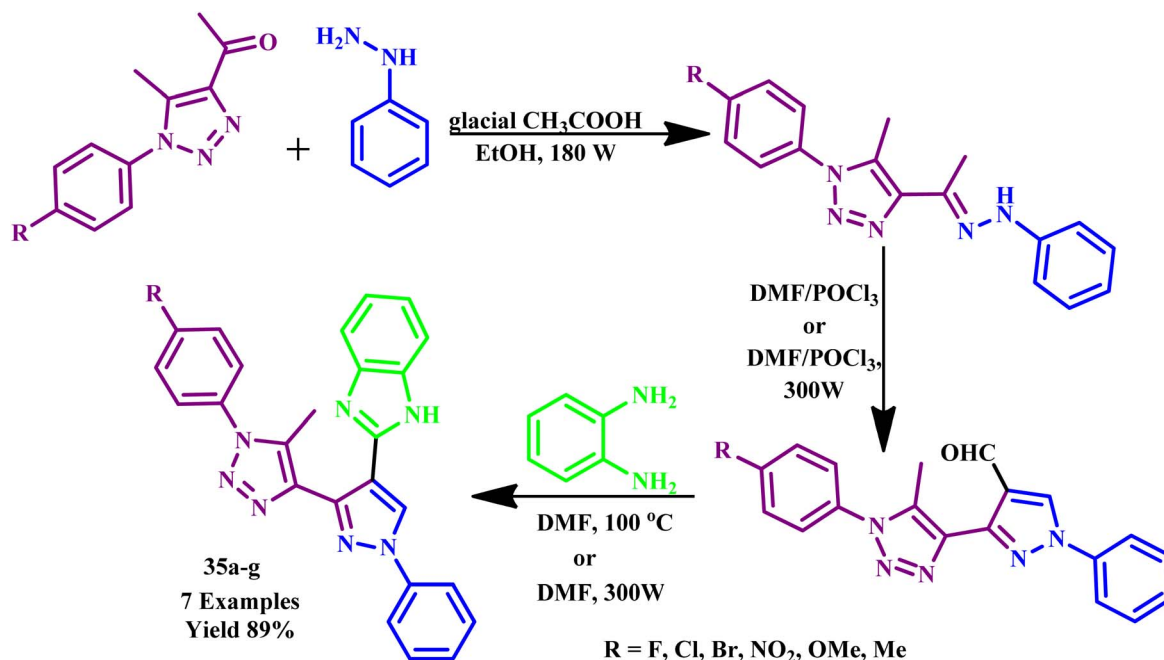
Scheme 25 Synthesis of 1,2,3-triazole derivatives (33a–p) from alkynes and trimethylsilylazide under microwave.<sup>66</sup>



Scheme 26 Microwave-assisted synthetic protocol for silicon-based multidentate triazole scaffolds (**34a–e**).<sup>68</sup>

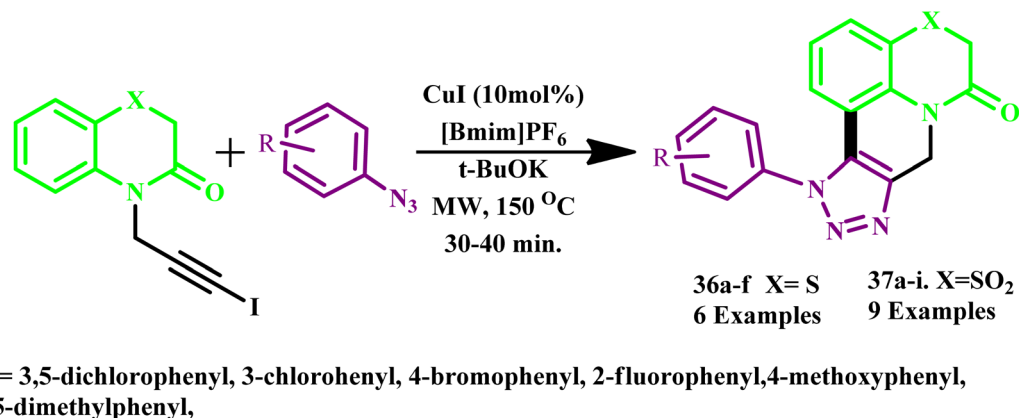
coumarin pharmacophores, as depicted in Scheme 40. They examined the antimicrobial and antimycobacterial properties of these compounds. Using traditional methods, the reaction mixture was stirred for 24 hours at 80 °C giving 52% product yield. However, when irradiated under microwave radiation at 180 W for 10.0 minutes, a 79% product yield was obtained. Notably, two derivatives exhibited outstanding antitubercular activities, with a minimum inhibitory concentration (MIC) of

1.56  $\mu\text{g mL}^{-1}$ , while other derivatives showed potential anti-bacterial activity against various bacterial and fungal strains. Structure–activity relationship studies revealed that a long lipophilic alkyl spacer with a carbon chain length of 5–8 and the presence of an electronegative chlorine atom at the C-6 position of the coumarin nucleus played essential roles in the broad range of biological activities observed in these compounds.<sup>80</sup>



Scheme 27 Microwave-assisted synthetic route for 3-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazole-4-carbaldehydes and benzimidazole derivatives (**35a–g**).<sup>69</sup>



Scheme 28 Synthetic protocol for the synthesis of fused 1,2,3-triazole derivatives (36a–f and 37a–i).<sup>70</sup>

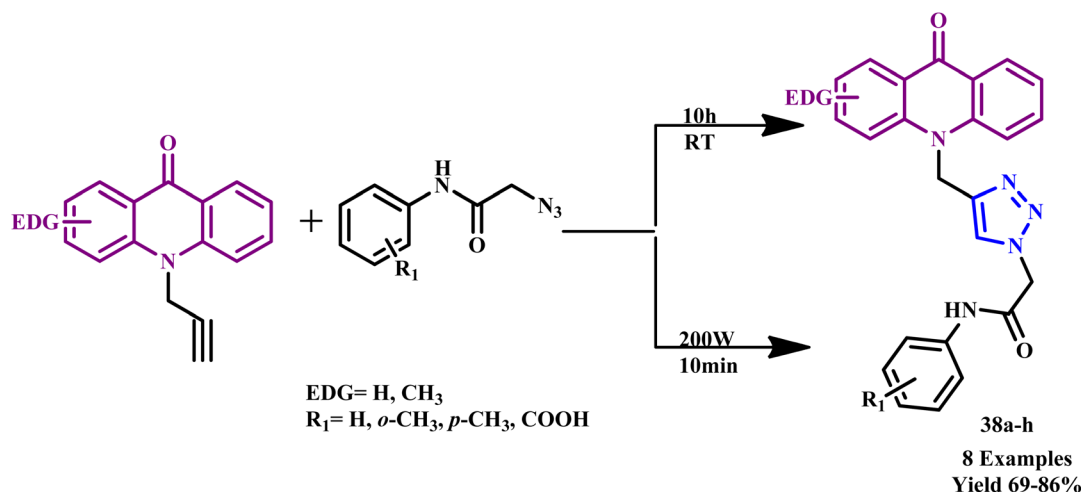
Similarly, Mohammed *et al.* reported perfluorobutylethylazide and 2,3,4,6-tetra-*O*-acetyl- $\beta$ -glucopyranosyl azides along with various terminal alkynes to create 1,2,3-triazoles using the microwave-assisted method.<sup>81</sup> Further, a small library of enantiopure  $\alpha$ -[4-(1-substituted)-1,2,3-triazol-4-yl] benzylacetamides derivatives (52a–h) (*R*) and (52a–h) (*S*) from racemic propargyl amines were synthesized by Castagnolo *et al.* using microwave-assisted Cu(I)-catalyzed click chemistry method (Scheme 41). These triazole derivatives are important and easily accessible intermediates for the synthesis of enantiopure azole analogues because they were synthesized in a short time with good yields and substantial enantiomeric excess.<sup>82</sup>

Librando developed a reproducible and straightforward synthetic procedure for recyclable Cu(I)–DAPTA complexes on carbon materials (such as carbon nanotubes (CNT) and activated carbon (AC)) to create a heterogeneous catalyst. These immobilized Cu(I)–DAPTA complexes were employed for catalytic synthesis of 1,2,3-triazole derivatives (53a–h) *via* cycloaddition reaction of azides and alkynes under microwave irradiation (Scheme 42). Microwave heating significantly

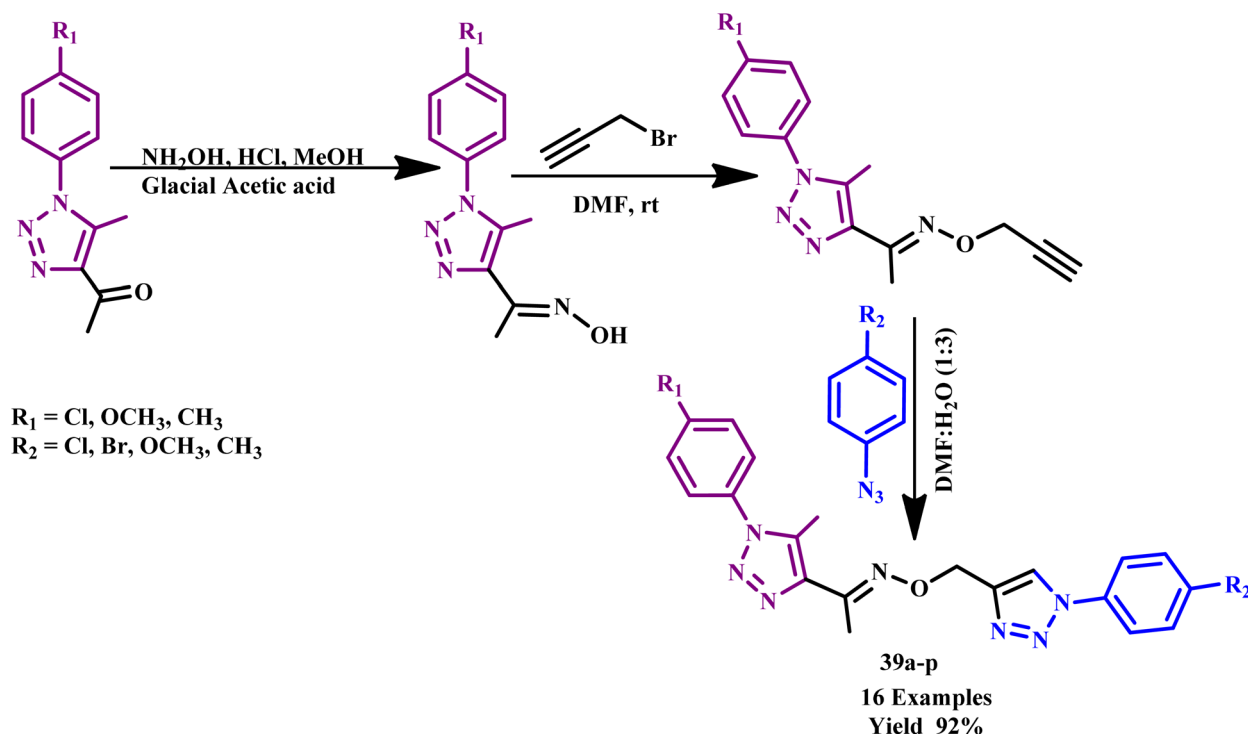
reduced reaction times compared to traditional methods and increased yield/purity of product by minimizing unfavorable side reactions.<sup>83</sup>

Dharavath *et al.* utilized microwave irradiation to develop a highly effective and environmentally friendly method for creating 1,4-disubstituted 1,2,3-triazole derivatives (54a–i) based on coumarin. This method employs a Cu(I)-catalyzed click reaction involving terminal alkynes and various substituted aryl azides (Scheme 43). The author reported that compared to the conventional approach (which required 6.0 hours and 72% yield), this innovative approach was simpler and more efficient and offered the advantages of high yields (90%) and a shorter reaction time (7 minutes). Additionally, some of the synthesized compounds exhibited good hydrogen-bonding interactions with Val-191 and His-88 amino acids as well as with water molecules, indicating their potential for biological activity.<sup>84</sup>

Alves *et al.* developed a metal-free, one-pot method for the synthesis of multiple 4-aryl-1,4-dihydrochromene-triazoles derivatives (55a–o) using PEG 400 as a solvent under microwave irradiation conditions, as illustrated in Scheme 44. This

Scheme 29 Synthetic route for a novel series of acridone-based 1,2,3-triazole hybrid derivatives (38a–h).<sup>71</sup>



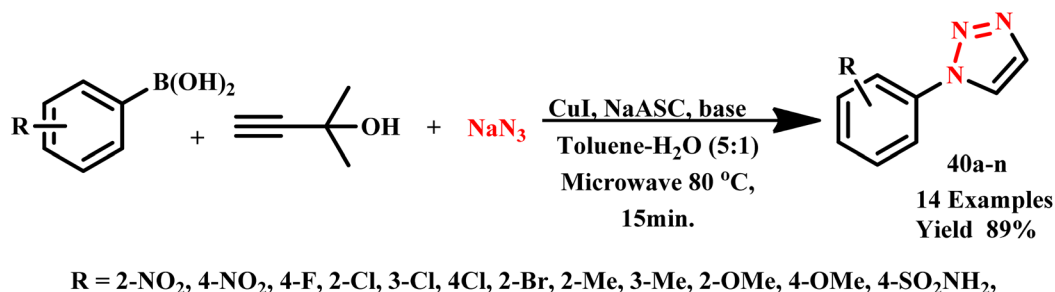
Scheme 30 Synthesis of 1,2,3-triazole derivatives (39a–p).<sup>9</sup>

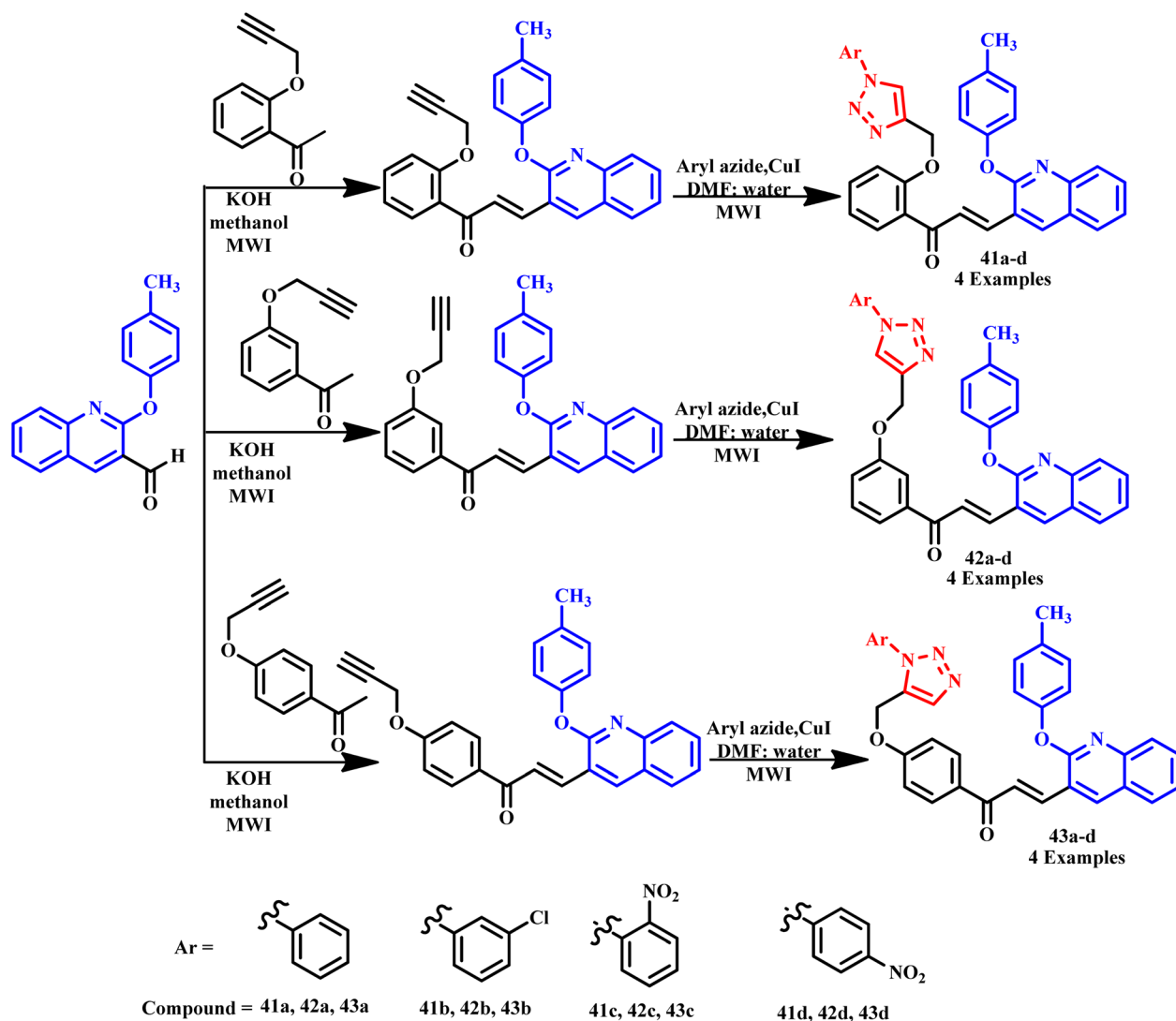
innovative approach leverages microwave irradiation to produce triazole compounds from readily available building blocks, achieving good yields and significantly reducing reaction times. The method was not only efficient but also environmentally friendly due to the use of PEG400 as a green solvent. Additionally, microwave-assisted synthesis ensures better control over reaction parameters, minimizing side reactions and enhancing product purity. This technique showcases the potential for the rapid and sustainable synthesis of biologically active compounds.<sup>85</sup>

Dutta *et al.* established a green method for synthesizing various 5-amino-1,2,3-triazoles from phenyl azide derivatives and benzyl cyanide. This innovative approach utilizes a bifunctional ionic liquid, [DHIM][OH], in combination with microwave irradiation conditions. The use of microwave heating not only accelerates the reaction but also enhances the overall efficiency and yield of the desired triazole products. This

method exemplifies sustainable chemistry by minimizing waste and utilizing environmentally friendly reagents, making it a valuable contribution to the field of organic synthesis. Furthermore, the versatility of ionic liquid as a solvent allows for easy recovery and reuse, promoting the principles of green chemistry.<sup>86</sup> Costa produced 4-substituted-1,2,3-triazolyl 1'-homo-3'-isoazannucleosides derivatives (56a–k)(±) –3 (±) –14 through MW assist cycloaddition reaction through different alkyne with 3,5-disubstituted proline derivative, as shown in Scheme 45. The compounds were tested *in vitro* for their cytotoxic effects on human ovary carcinoma cell lines (A2780), human lung cancer cell lines (NCI-H460) and human breast carcinoma cell lines (MCF-7). Compounds **61f** (±) –8 and **61g** (±) –9 exhibited inhibitory activity, with IC<sub>50</sub> values of 56 and 942 mM against the A2780 cell lines.<sup>87</sup>

Further, Garg and his coworker established a microwave-induced multicomponent reaction from nitroalkane, aldehyde

Scheme 31 Synthesis of 1-monosubstituted 1,2,3-triazole (40a–n).<sup>72</sup>

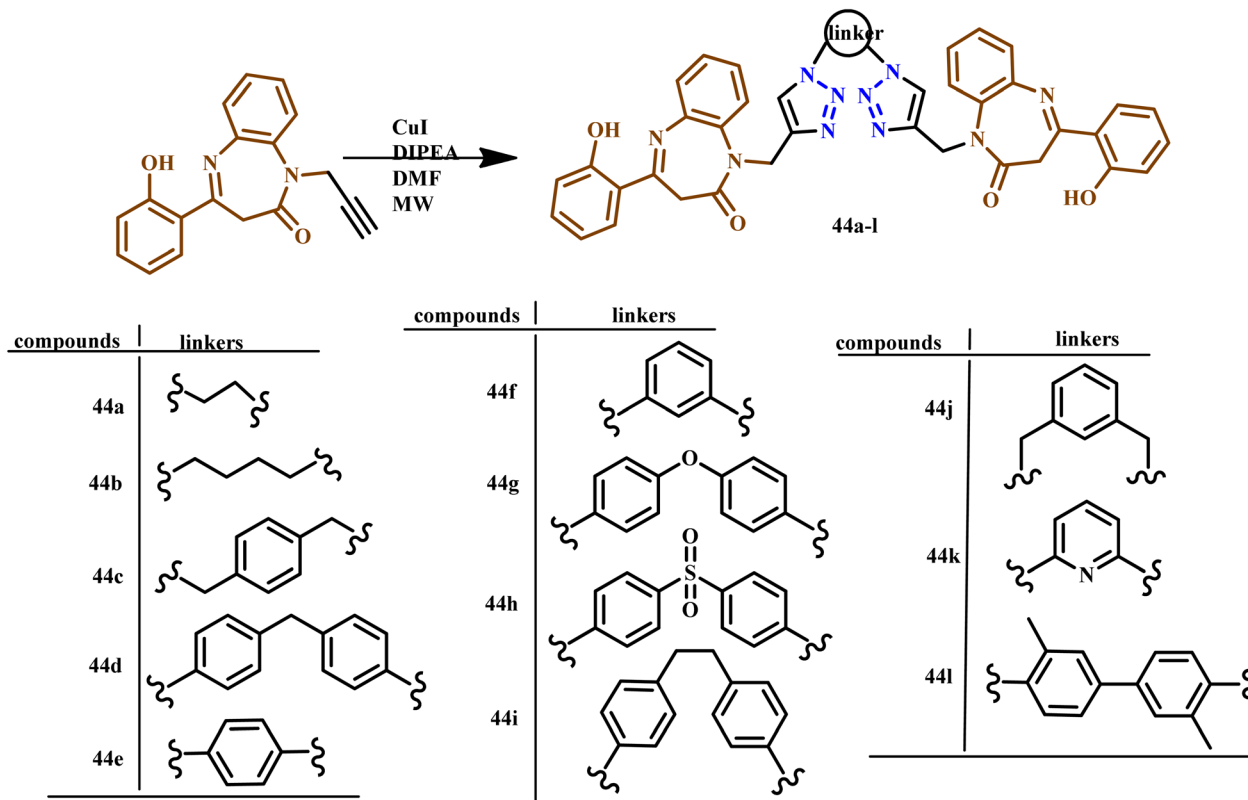
Scheme 32 Synthesis of *p*-tolylloxyquinoline-triazole hybrid compounds (41a–43d).<sup>4</sup>

and sodium azide in polyethylene glycol 400 to produce biologically significant 4-aryl-NH-1,2,3-triazole derivatives (57a–q) using anthranilic acid as a catalyst. The protocol was optimized using inexpensive and easily accessible reagents. The reported protocol gave excellent product yields, metal-free conditions, use of MW irradiation as an unconventional energy source, gram scale synthesis and easy solvent recycling (Scheme 46).<sup>88</sup>

Further, He *et al.* developed a straightforward procedure for the effective and rapid synthesis of difunctional glycosyl triazolyl acids using a click reaction facilitated by microwave irradiation. This innovative approach allows for the efficient production of glycosyl mono-, di- and tyrosine derivatives, which were identified as novel inhibitors of PTP1B and demonstrated selectivity over other homologous protein tyrosine phosphatases several fold. The significant selectivity and effectiveness of these synthesized compounds highlighted their potential for therapeutic applications, particularly in targeting diseases related to dysregulated PTP activity.<sup>89</sup> Iwasaki *et al.* developed an efficient method for the direct arylation of 1,4-

disubstituted 1,2,3-triazole derivative (58a–q) using aryl chloride in the presence of palladium, employing microwave irradiation at 250 °C for 15 minutes, as illustrated in Scheme 47. This method successfully synthesizes several 1,4-disubstituted 1,2,3-triazoles through copper-catalyzed [3 + 2] cycloaddition of terminal alkynes and organic azides. The present procedure not only provides a clear and rapid pathway for synthesizing 1,4,5-trisubstituted 1,2,3-triazoles but also enhances overall yield and purity. This advancement underscores the potential of microwave-assisted techniques in streamlining synthetic processes and expanding the utility of triazole derivatives in pharmaceutical applications.<sup>90</sup>

Joosten *et al.* reported microwave-assisted regioselective synthesis of multivalent 1,4-disubstituted 1,2,3-triazole-linked glycodendrimers (59a–s) through a copper-catalyzed [3 + 2] cycloaddition process, achieving excellent yields. By utilizing microwave irradiation, azido carbohydrates were effectively linked to dendritic acetylenes *via* a CuI-catalyzed reaction, as shown in Scheme 48. The method streamlined synthesis and



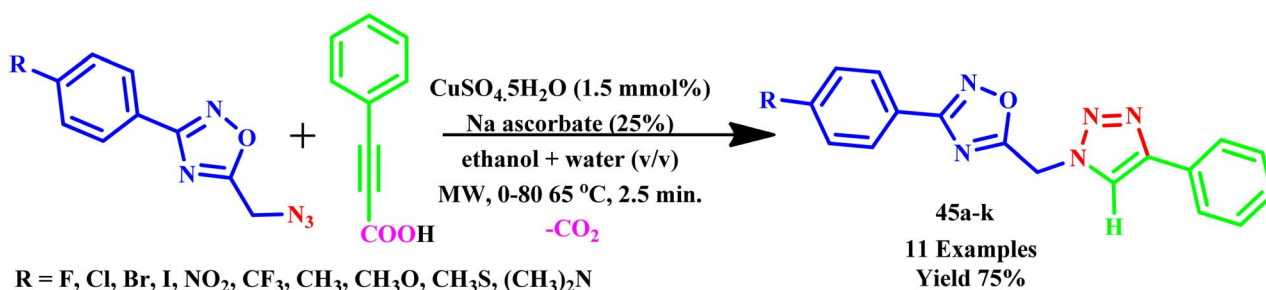
Scheme 33 Microwave-assisted synthesis of 1,1'-(1,1'-(hexane-1,6-diyl)bis(1H-1,2,3-triazole-4,1-diyl) bis(methylene))bis(1,5-benzodiazepin-2-one) and 1-((1-(6-azidoheptyl)-1H-1,2,3-triazol-4-yl)methyl)-(1,5-benzodiazepin-2-one) (44a-i).<sup>73</sup>

enhanced the efficiency of the process, resulting in yields of up to 98% when conducted at 80 °C for 20 minutes. Additionally, two glycoconjugates incorporating fluorescent labels were developed, which are essential for the biological evaluation of these molecules.<sup>91</sup>

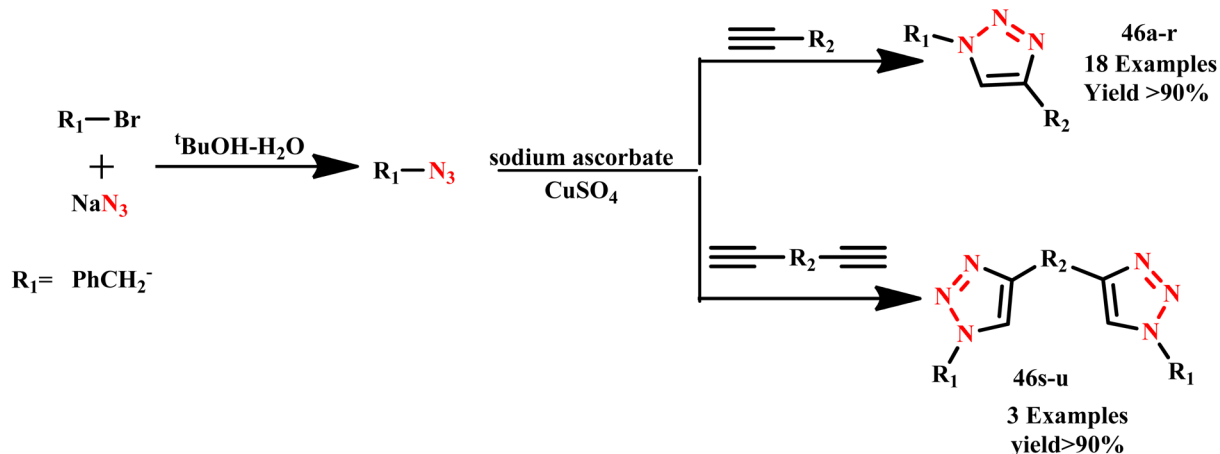
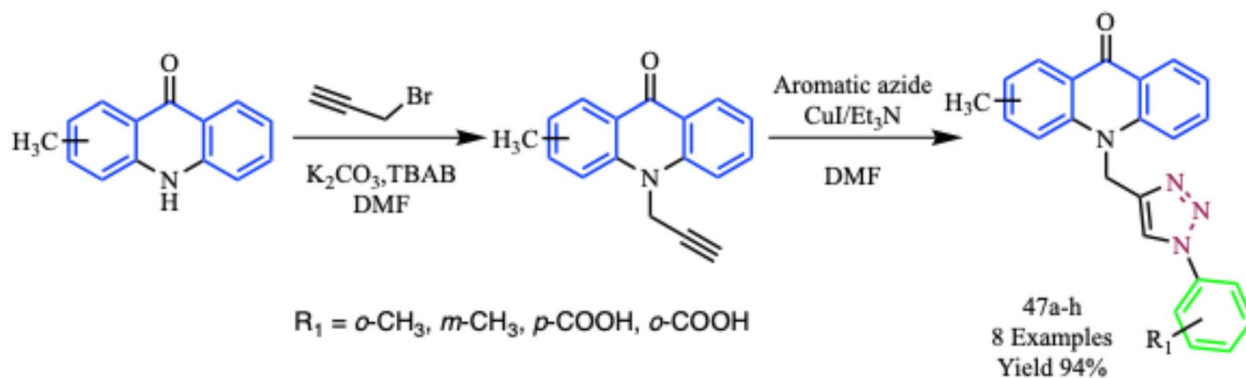
Sravanthi *et al.* synthesized (*E*)-NO-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-3-(4-phenyl-1H-1,2,3-triazol-1-yl) benzohydrazide derivatives (60a-l) under microwave irradiation and conventional conditions (Scheme 49). The microwave irradiation approach offered simpler, straightforward and environmentally friendly synthesis with shorter reaction times and higher yields. Most heteroaryl benzohydrazide derivatives were synthesized using this approach, which offers diverse environmental flexibility. However, the traditional method reaction was

completed within 1–2 h with an 80% yield, while the MW-assisted reaction took only 4–6 minutes with a 98% yield. In addition, compound 60e and 60g derivatives showed a significant broad spectrum of activities against both Gram-positive and Gram-negative bacterial strains.<sup>92</sup>

J. Li *et al.* synthesized 5-[[1-(benzyl-1H-1,2,3-triazol-4-yl)methoxy]methyl]-3-(4-substituted-phenyl)isoxazole derivatives (61a-i) and substituted 2-[[4-[[3-(phenylisoxazol-5-yl)methoxy]methyl]-1H-1,2,3-triazol-1-yl)methyl]-2-[[5-[[3-(phenylisoxazol-5-yl)methoxy]methyl]-1H-1,2,3-triazol-1-yl)methyl]propane-1,3-diol compounds *via* click reaction under MW irradiation using copper(i) ion as catalyst, which was prepared *in situ* from sodium ascorbate and copper acetate, as depicted in Scheme 50. Compared to the conventional method, the microwave

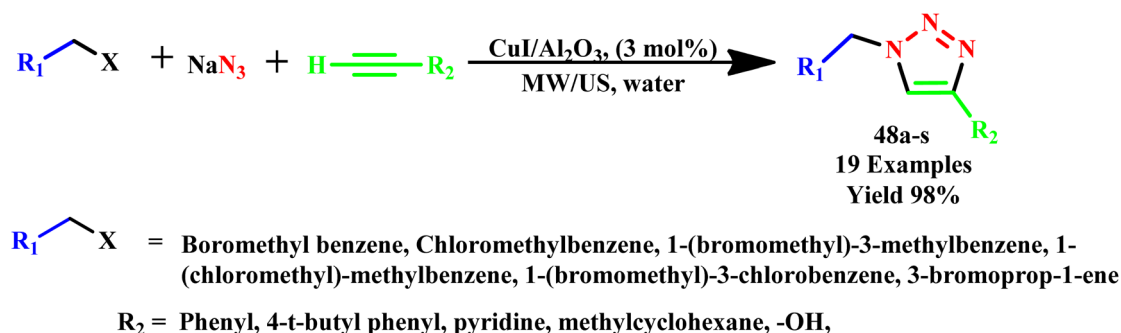


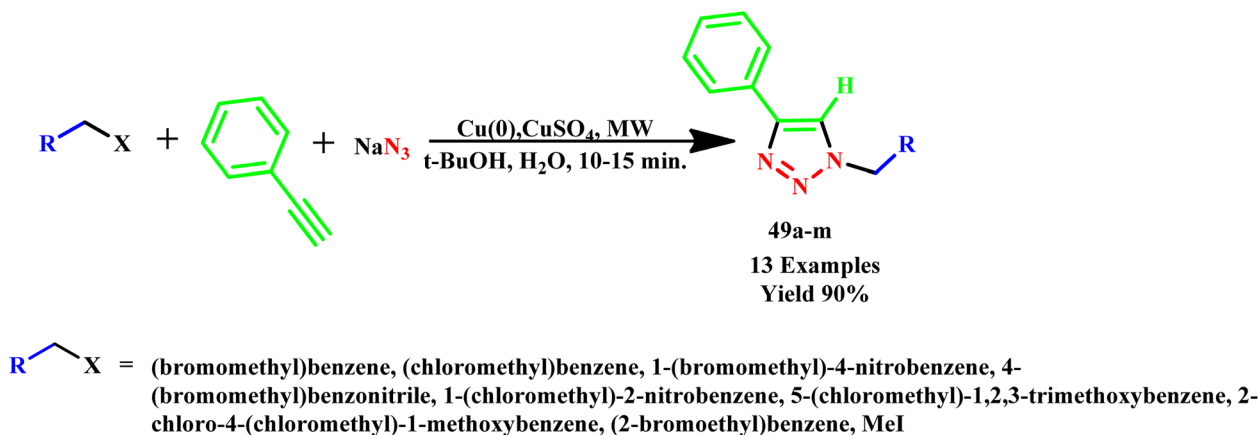
Scheme 34 Synthesis of 1,2,4-oxadiazol-5-ylmethyl-1,2,3-triazoles (45a-k) *via* 1,3-dipolar cycloadditions of azide and phenyl propiolic acid.<sup>64</sup>

Scheme 35 Microwave-assisted synthetic route for 1,4-disubstituted 1,2,3-triazole derivatives (46a–u).<sup>74</sup>Scheme 36 Microwave-assisted synthesis of 1,2,3-triazole derivatives (47a–h) from acridone.<sup>75</sup>

irradiation method offers a shorter reaction time and a higher yield. The conventional method required 9–10 hours to complete with a 69% yield, while the MW-assisted reaction was completed within 10.0 minutes with a 93% yield.<sup>93</sup>

Zabrodski developed a quick and effective way to incorporate 2-(1*H*-1,2,3-triazol-4-yl)pyridine and 2-(1*H*-1,2,3-triazol-1-ylmethyl)-pyridine into *N*-substituted glycine peptidoligomers via an alkyne–azide click reaction on a solid support under microwave irradiation. The novel peptoid chelator was used to

Scheme 37 Microwave-assisted synthesis of 1,4-disubstituted 1,2,3-triazoles (48a–s) via  $CuI$  on  $Al_2O_3$  catalyzed.<sup>76</sup>

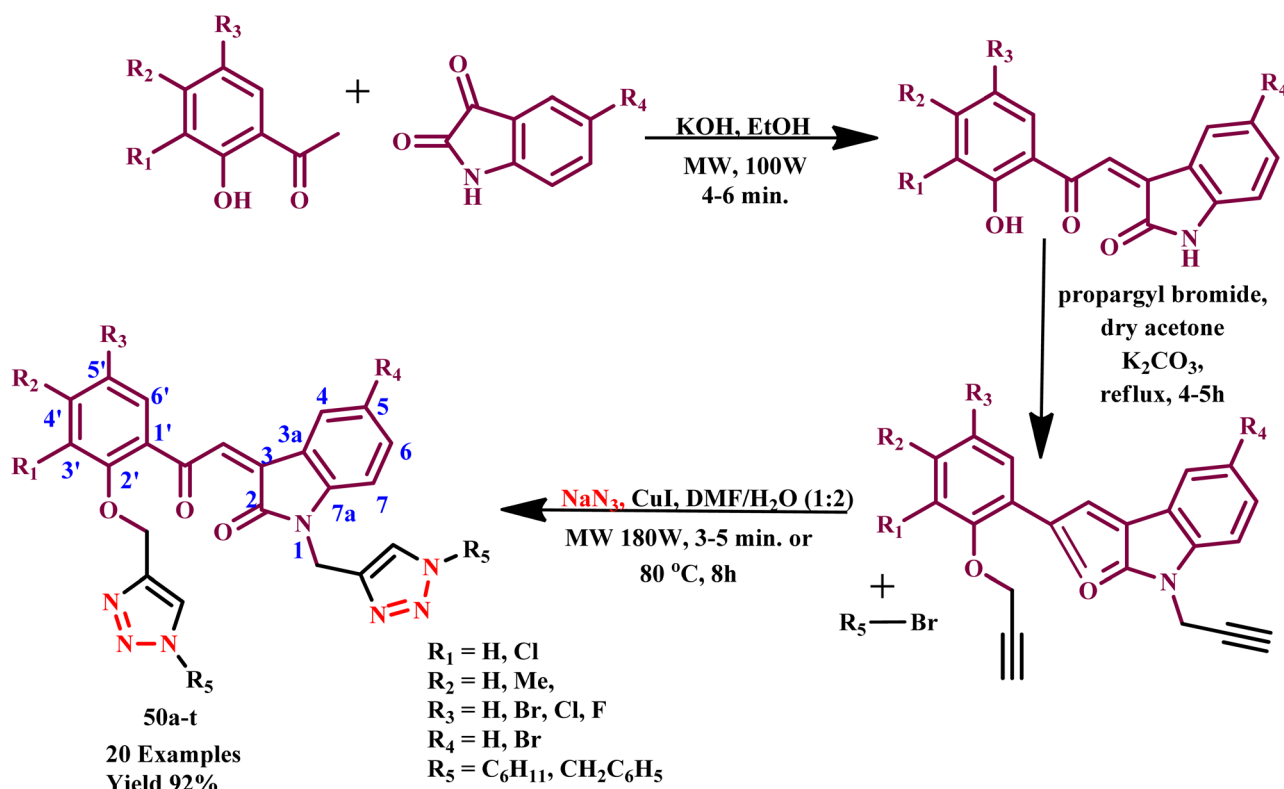


Scheme 38 Microwave-assisted synthetic route for 1,4-disubstituted 1,2,3-triazoles (49a-m).<sup>77</sup>

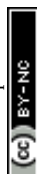
create intermolecular and intramolecular chiral helical peptoid-copper(II) complexes.<sup>94</sup> Similarly, a novel, highly effective, solvent and metal free three-component green synthesis of 5-(1,3-thiazolan-2-yl)-1*H*-1,2,3-triazoles and element-substituted NH-1,2,3-triazoloimines derivatives (**62a-d**) was developed by Medvedeva *et al.* using 3-silicon(germanium)-substituted 2-propyn-1-als functionalized primary amine and trimethylsilyl azide through MW irradiation (Scheme 51). The reported MW-assisted process required 10.0 minutes at 100 °C to obtain the target product with 92% yield, and at room temperature with

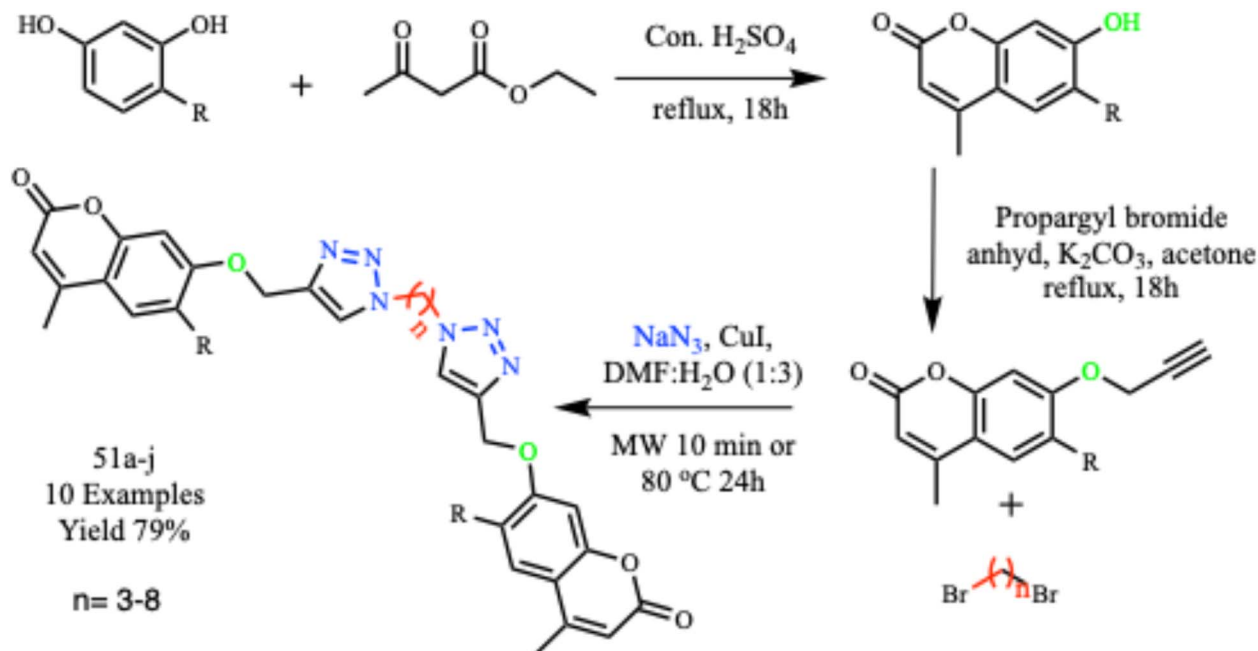
stirring, the same reaction required 10.0 days for completion. The advantages of this approach include the accessibility of a straightforward experimental process, great product yields and fast reaction time.<sup>95</sup>

The 1,2,3-triazole and isoxazole derivatives-based flavonoids were developed by Ashok and his coworker using microwave irradiation and traditional heating techniques. The research group reported that using streptomycin as a reference medication, these compounds exhibit excellent action against Gram positive pathogens, such as *Staphylococcus aureus*, *Bacillus*



Scheme 39 Microwave-assisted synthetic route for 2-indolinone-based bis-1,2,3-triazole (50a-t) synthesis.<sup>79</sup>

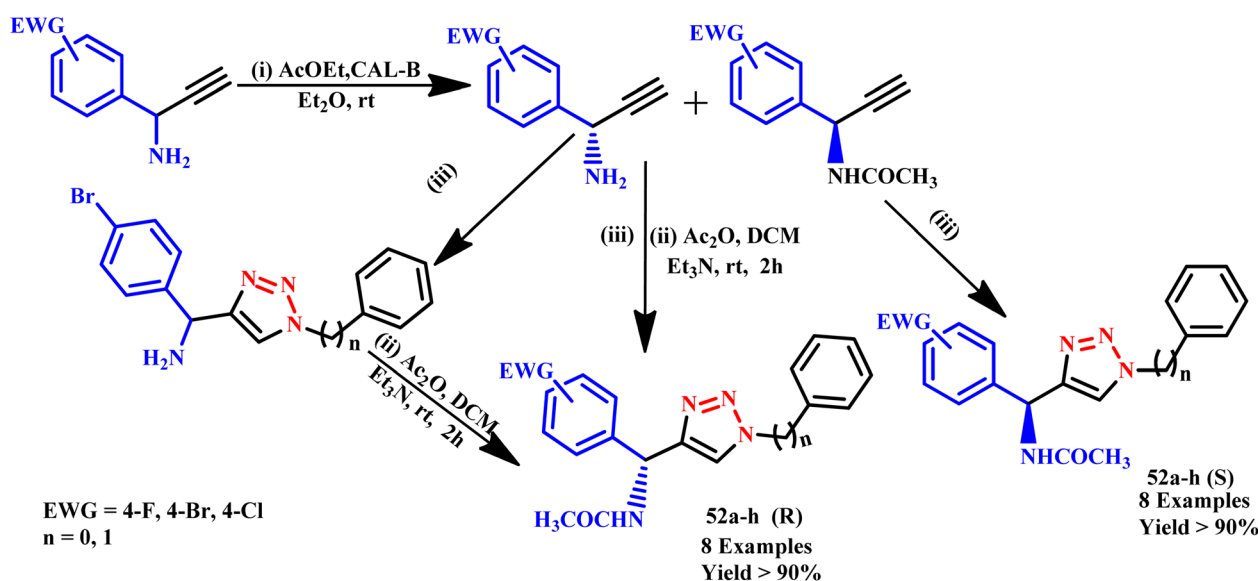




Scheme 40 Synthesis of dimers of coumarin-tethered 1,2,3-triazole hybrids (51a-j).<sup>80</sup>

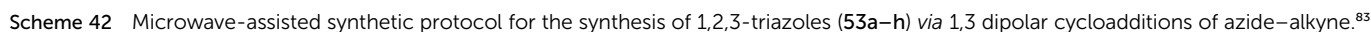
*subtilis*, and Gram-negative organisms, such as *Pseudomonas aeruginosa* and *Escherichia coli*. The reported product showed the ability to scavenge free radicals examined using ascorbic acid as a reference medication. HeLa cell lines and MCF-7 were used for testing anticancer activities.<sup>96</sup> Further, a novel class of tridentate ligands was prepared using microwave irradiation to synthesize diversely functionalized pyridyl-1,2,3-triazole derivatives without the need for metals or azides by Gullledge and coworkers. The typical work uses *N*-tosylhydrazones and

anilines as feasible synthetic substitutes and avoids the use of thermally sensitive and poisonous organoazides.<sup>97</sup> Mnasri and his coworkers synthesized Cu-doped rod-shaped mesoporous silica nanoparticles (Cu-SN) and used them as an effective heterogeneous catalyst for the synthesis of 1,4-dibustituted-1,2,3-triazole derivatives *via* a 1,3-dipolar cycloaddition reaction in aqueous solution through a microwave irradiation procedure at 45–80 °C and obtained up to 98% yield. The synthesis of 1,4-dibustituted-1,2,3-triazole derivatives in



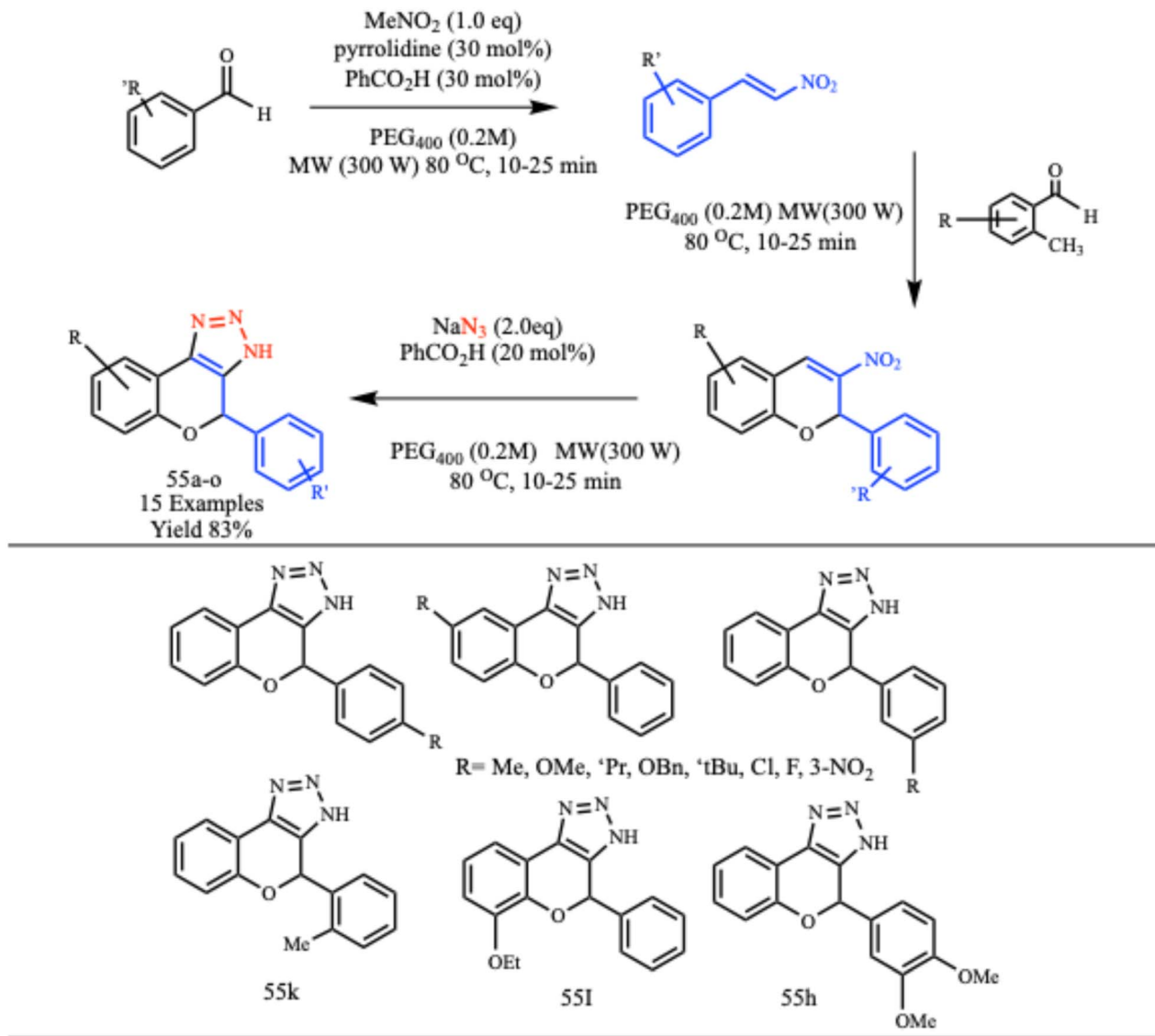
Scheme 41 Microwave-assisted synthesis of a-[4-(1-substituted)-1,2,3-triazol-4-yl]benzylacetamides. Conditions: (iii) (for  $n = 1$ )  $\text{NaN}_3$ , benzyl chloride, sodium ascorbate/ $\text{Cu}(\text{SO}_4) \cdot 4\text{H}_2\text{O}/t\text{-BuOH}$ , MW, 125 °C, 10 min; (for  $n = 0$ )  $\text{pHn}_3$ , sodium ascorbate/ $\text{Cu}(\text{SO}_4) \cdot 4\text{H}_2\text{O}/t\text{-BuOH}$ , MW, 120 °C, 10 min.<sup>82</sup>





a low reaction time. The research group found that compared to standard drugs chloramphenicol and ampicillin, some of the derivatives exhibited excellent inhibitory activities against *P. aeruginosa* and greater effectiveness against the albicans fungus strain. A molecular docking study was also conducted to comprehend the binding interaction with a protein. Compound (**63d**) displayed outstanding inhibitory activities against *P. aeruginosa* compared to reference/standard drugs chloramphenicol and ampicillin. Compound **63b** exhibited better potency





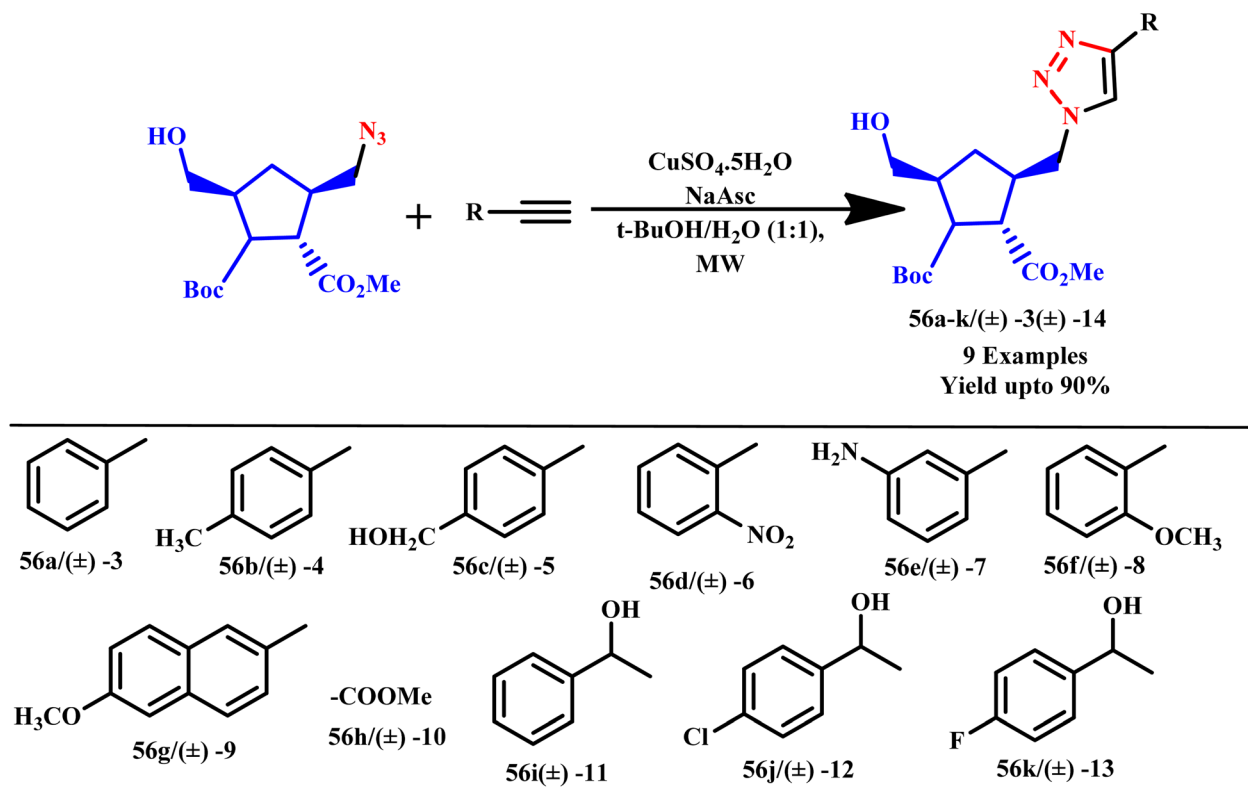
Scheme 44 Microwave-assisted protocol for the synthesis of 4-aryl-1,4-dihydrochromene-triazoles (55a-o).<sup>85</sup>

against fungi strain *C. albicans* compared to the reference drugs fluconazole and griseofulvin. Further, it was observed that the reaction at room temperature takes 120.0 minutes at 100 °C for completion, while ultrasonic-MW 100 W took 15.0 minutes and microwave irradiation took 15–30 minutes at 100 W to obtain the desired product.<sup>99</sup>

Similarly, an efficient microwave-assisted 1,3-dipolar cycloaddition reaction between 9-bromophenanthrene and sodium azide (NaN<sub>3</sub>) in the presence of potassium *tert*-butoxide facilitated the one-pot synthesis of 1*H*-phenanthro[9,10-*d*][1,2,3]triazole (64), as illustrated in Scheme 53. Notably, this protocol demonstrated significant efficiency, shorter reaction time (45 seconds), and high product yield (62%), while traditional methods required much longer reaction times. This rapid synthesis highlights the advantages of microwave irradiation in organic transformations. It was suggested that under these reaction conditions, 9-bromophenanthrene was converted to

benzynes intermediate, which subsequently participated in the cycloaddition with azide, underscoring the innovative mechanistic insights gained from this approach.<sup>100</sup>

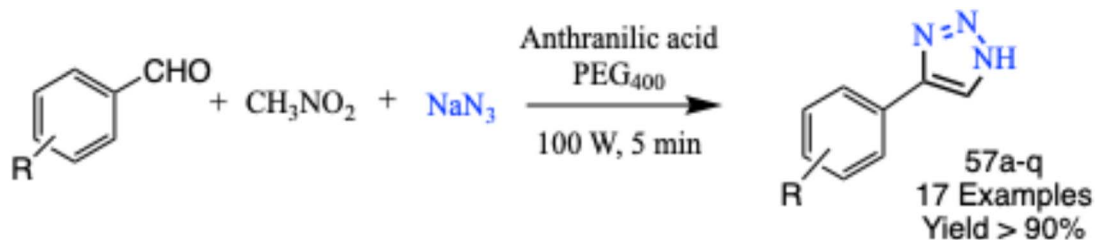
In a recent report, H. Naeimi *et al.* described the copper@PMO-catalyzed synthesis of  $\beta$ -hydroxy-1,2,3-triazoles derivatives (65a-o) via multicomponent reaction under microwave irradiation at 277 W for just 7.0 minutes, achieving an impressive yield of 98% (Scheme 54). This protocol utilized solid-supported catalyst and microwave energy and offered numerous advantages, such as cost-effectiveness, environmentally friendly reaction conditions, non-toxic reagents, high conversion rates and significantly reduced reaction times. Furthermore, the catalyst was easily recyclable and demonstrated no leaching, contributing to the high product yields. This approach enhances the efficiency of synthesis and aligns with the principles of green chemistry, making it a valuable advancement in organic synthesis.<sup>101</sup>

Scheme 45 Microwave-assisted synthesis of triazoles.<sup>87</sup>

Similarly, Potewar *et al.* developed a microwave-assisted protocol for synthesizing novel 1-(1',2,3,3',4,4',6-hepta-O-acetyl-6'-deoxy-sucrose-6'-yl)-4-substituted-1,2,3-triazoles derivative (**66a-j**) through Cu-catalyzed 1,3-dipolar cycloaddition of sucrose-derived azides and terminal alkynes and achieved higher yields and reduced reaction times (Scheme 55). This innovative approach resulted in the creation of a diverse library of 1,2,3-triazole-sucrose conjugates (**66a-j**) by integrating structural motifs from carbohydrates and triazoles. The compound 1',2,3,3',4,4',6-hepta-O-acetyl-6'-azido-6'-deoxy-sucrose was regioselectively synthesized from sucrose using an improved procedure and was employed in cycloaddition

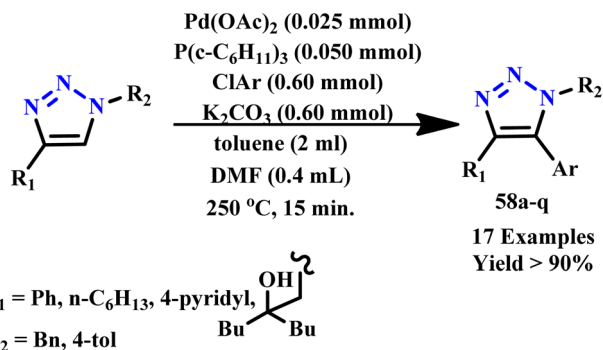
reactions. Remarkably, the microwave method yielded 94% of the target product within just 5.0 minutes at 400 W, while traditional methods required much longer reaction times. This advancement enhances the efficiency of synthesis and underscores the potential of microwave-assisted techniques in the development of complex glycosylated compounds.<sup>102</sup>

Sucharitha described an effective one-pot three-component Cu-catalyzed synthesis of benzo[1,3]thiazine-derived fused 1,2,3-triazole derivatives (**67a-m**) under MW conditions in ionic liquid (Scheme 56). It was found that the conventional method required a longer reaction time and high temperature and produced a poor yield (140 °C, 20 h and 45% yield) compared to



**R** = 4-bromophenyl, 4-chlorophenyl, 4-methoxyphenyl, phenyl, 2-chlorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 4-CN-phenyl, 2-nitrophenyl, 4-hydroxyphenyl, 4-fluorophenyl, 3-nitrophenyl, 3-bromophenyl, 2,4-dichlorophenyl, 2-chloro-6-fluorophenyl, furan, thiophene

Scheme 46 Microwave-assisted synthesis route for 4-aryl-NH-1,2,3-triazoles (**57a-q**).<sup>88</sup>



Scheme 47 Microwave-assisted Pd catalyzed arylation of 1,4-disubstituted 1,2,3-triazole derivatives (**58a-q**).<sup>90</sup>

the MW method (140 °C, 30 min. and 81% yield). The advantage of this method is a simple workup process, high yields and quick reaction times. It was observed that when compared to standard medicine, these reported compounds exhibited potent efficacy and showed considerable effect on biofilm inhibition. Some of the reported derivatives also exhibited a two-fold increase in inhibitory activity (MIC value of  $3.12 \mu\text{g mL}^{-1}$ ) against *S. epidermidis* and *B. subtilis* compared to standard ciprofloxacin ( $6.25 \mu\text{g mL}^{-1}$ ) against tested bacteria and showed equipotent activities against *S. aureus* (MIC value of  $6.25 \mu\text{g mL}^{-1}$ ) in comparison to the positive control. Promising results were obtained using conjugates of series against *S. aureus* and *E. coli*, with an MIC value of  $6.25 \mu\text{g mL}^{-1}$ , which is equivalent to ciprofloxacin. The findings indicate that the two derivatives are effective inhibitors of *B. subtilis* and *S. aureus* biofilm growth and strong antibacterial agents.<sup>103</sup>

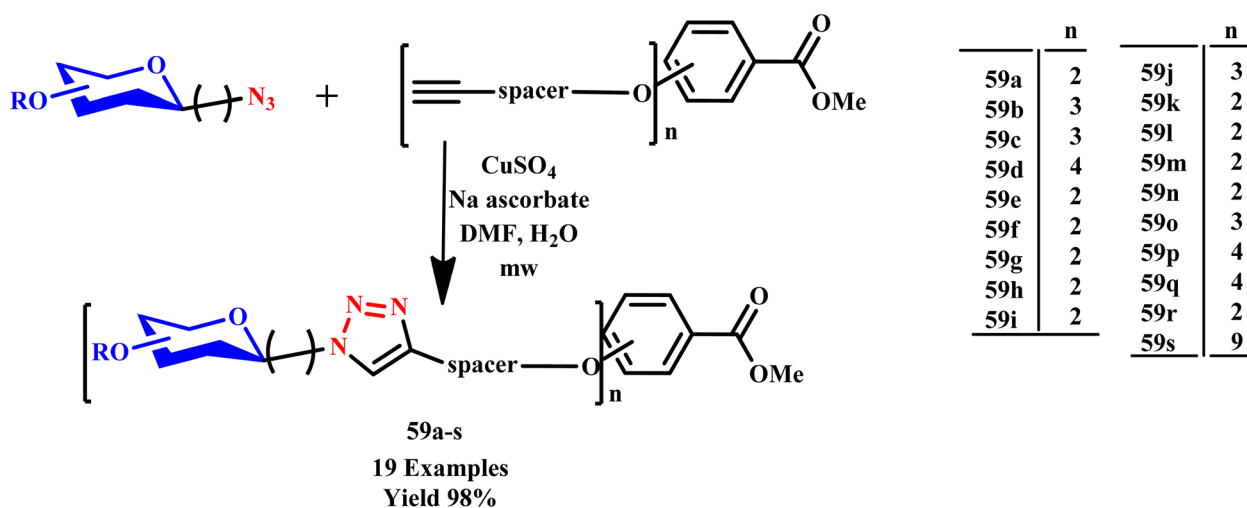
Reddy and coworkers reported unique hybrids of benzofuran-based triazole analogues (**68a-f**) using both traditional methods and microwave irradiation methodology (Scheme 57). They reported that the MW irradiation methodology was more environmentally friendly, quick, easy and high

yielding. In the conventional method, the reaction was completed in 23–24 hours at room temperature and produced a lower amount of yield (65–67%), while under microwave irradiation conditions, it produced the desired product within 6–8 minutes at 180 W with 86–89% yield. The prepared compounds were tested for their *in vitro* antibacterial activity against the Gram positive bacterial strains of *Bacillus subtilis*, *Staphylococcus aureus*, and Gram negative bacterial strains of *Klebsiella pneumoniae* and *Escherichia coli* at two separate concentrations of 20 and  $40 \mu\text{g mL}^{-1}$ . In this case, compounds **68a**, **68b**, and **68f** showed maximum zone inhibition against the tested bacterial strains.<sup>104</sup>

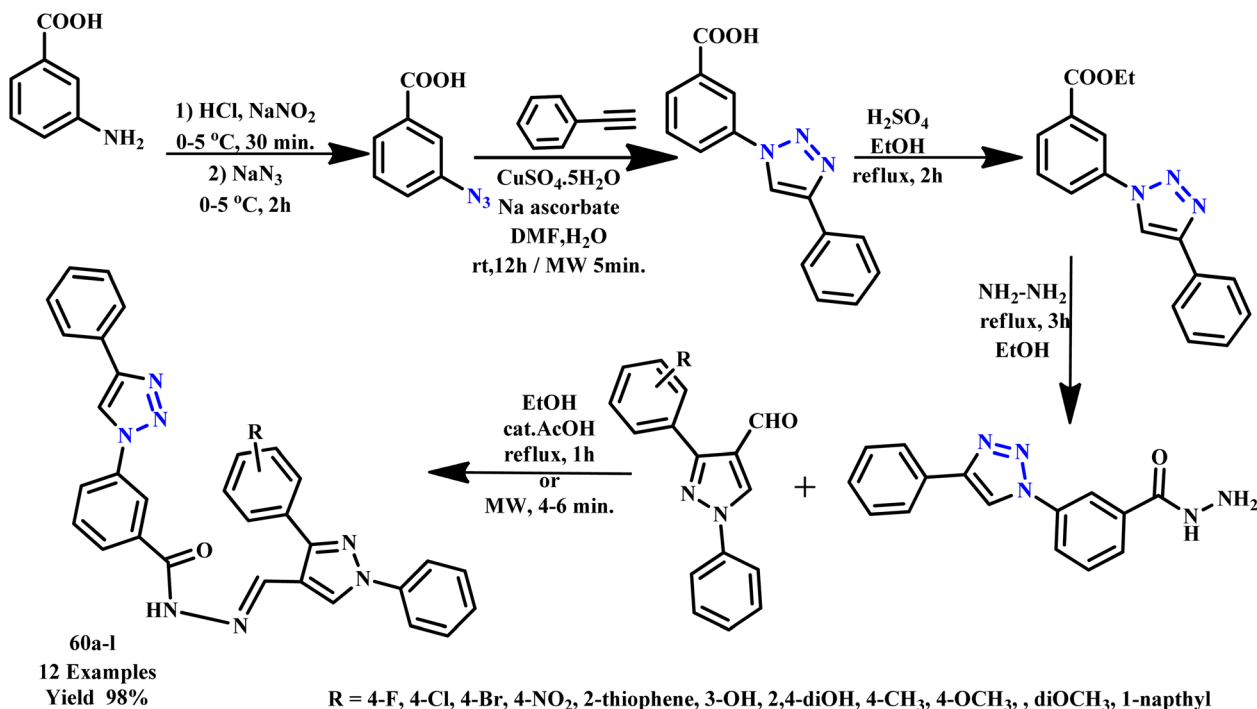
Znati *et al.* designed and synthesized a new series of 1,4-disubstituted triazole-linked flavonol derivatives (**69a-x**) via a combination of the library of variably substituted aryl azides and three cytotoxic flavonols under microwave irradiation conditions with 78–93% yield within 5 minutes (Scheme 58). The newly synthesized compounds were tested for their cytotoxic activities against three different human cancer cell lines, including breast (MCF-7), ovarian (OVCAR-3), and colon (HCT-116). It was found that reported compounds **69c** and **69p** demonstrated excellent activity against OVCAR-3 and compounds **69f**, **69g** and **69q** showed high activity against HCT-116 with  $\text{IC}_{50}$  values <  $3.0 \mu\text{M}$ .<sup>105</sup>

In another report, Saikia *et al.* reported the microwave-assisted regioselective synthesis of 1,4-disubstituted 1,2,3-triazole derivatives (**70a-m**) in methanol using a Cu(II) catalytic and ionic liquid under MW irradiation (Scheme 59). The synthesis of 1,2,3-triazole moieties in a one-pot multicomponent pathway was followed by *in situ* reduction of an ionic liquid-assisted Cu(II) catalyst to Cu(I). Additionally, it was shown that using microwave irradiation in the reported synthetic sequence resulted in a remarkable reduction in reaction times with outstanding yields and high selectivity.<sup>106</sup>

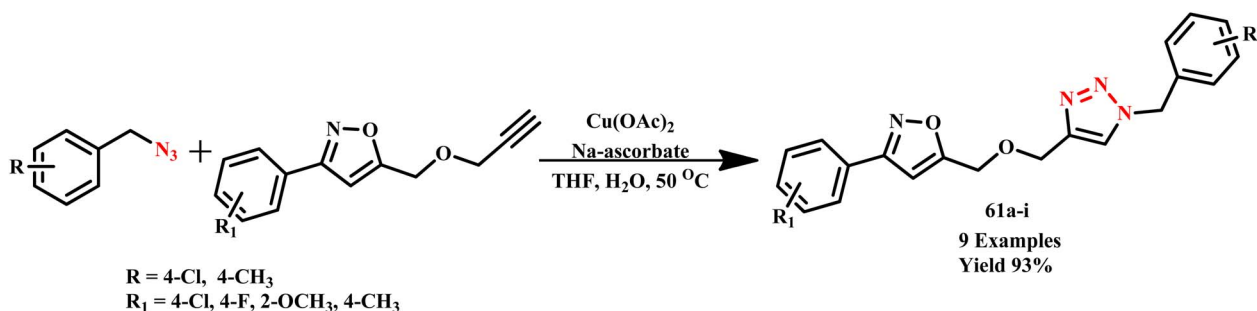
A series of highly symmetrical phthalocyanines (**71**) with eight peptide residues were developed by Sokolova and coworkers using a Cu(I)-catalyzed 1,3-dipolar cycloaddition



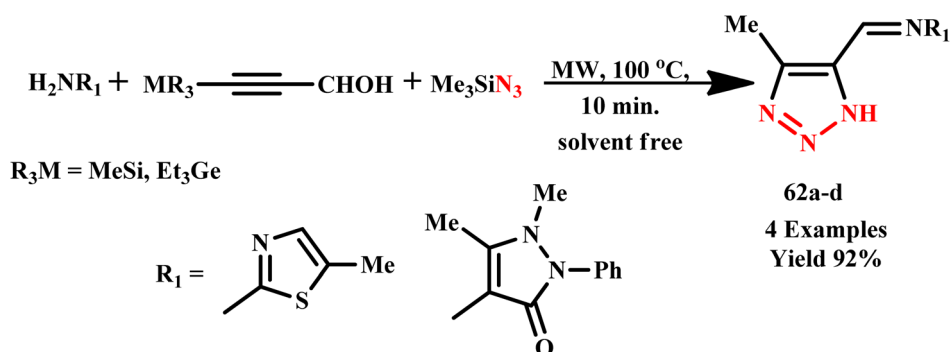
Scheme 48 Synthetic route of copper-mediated triazole glycodendrimers (**59a-s**).<sup>91</sup>



Scheme 49 Synthetic route for 3-(4-phenyl-1H-1,2,3-triazol-1-yl)benzohydrazide derivatives (60a–l).<sup>92</sup>



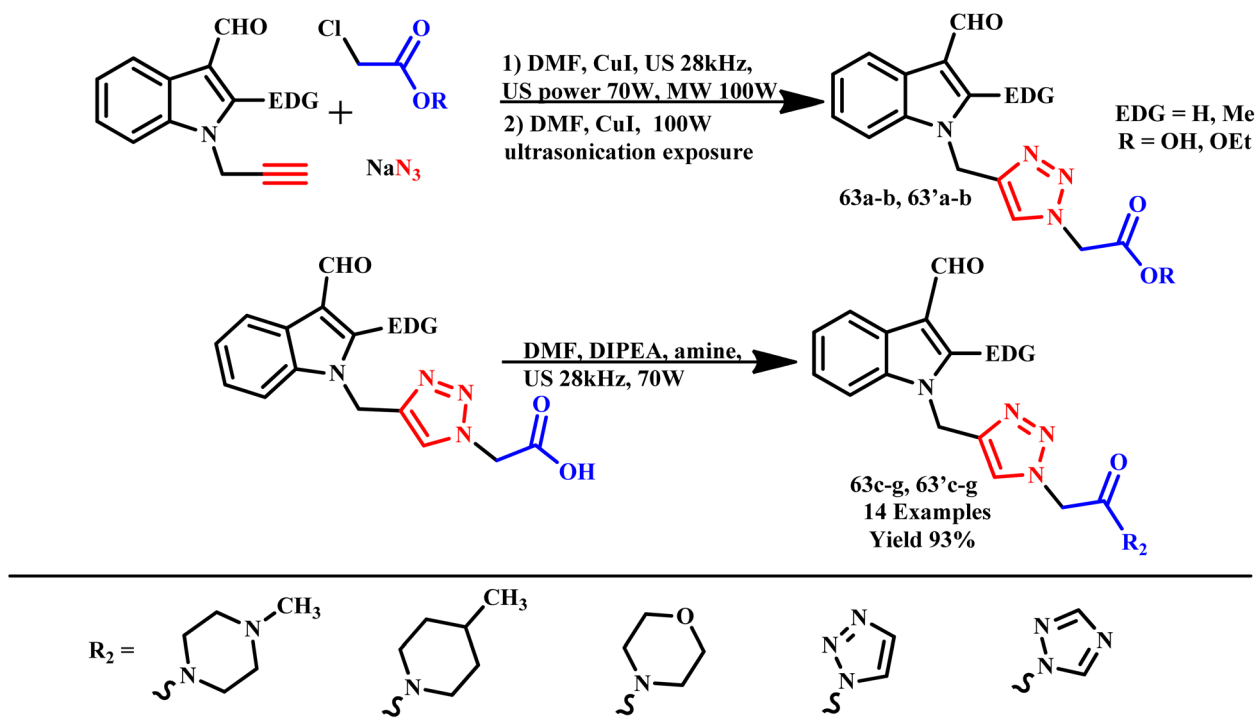
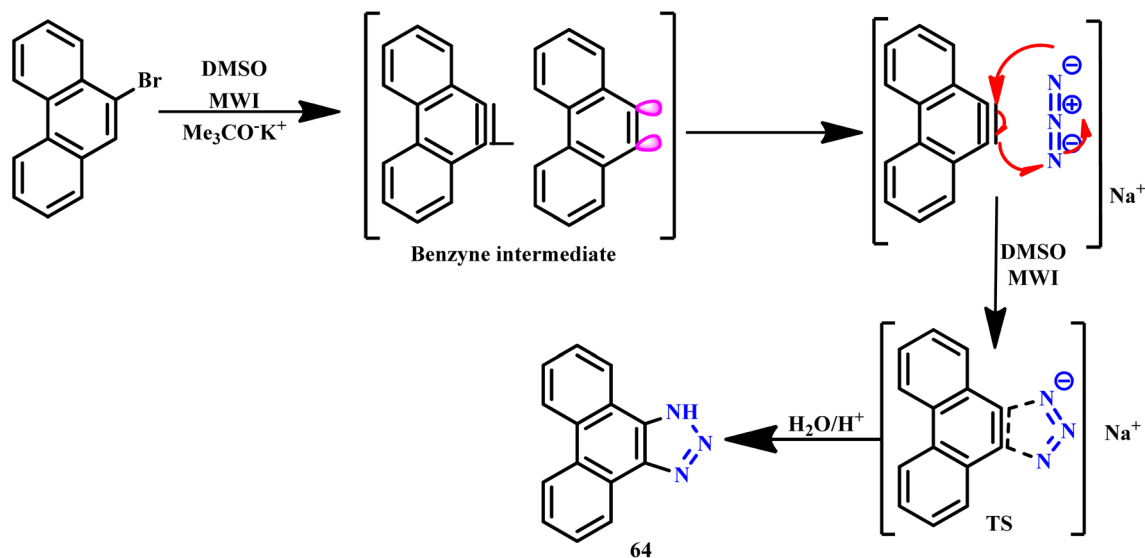
Scheme 50 Microwave-assisted synthetic route for single 1,2,3-triazole derivatives (61a–i).<sup>93</sup>



Scheme 51 Microwave-assisted synthesis of NH-1,2,3-triazoloinimes (62a–d).<sup>95</sup>

reaction under microwave irradiation (Scheme 60). The phthalocyanine conjugates were non-toxic in nature over the whole concentration range, making them potential therapeutic photosensitizers.<sup>107</sup>

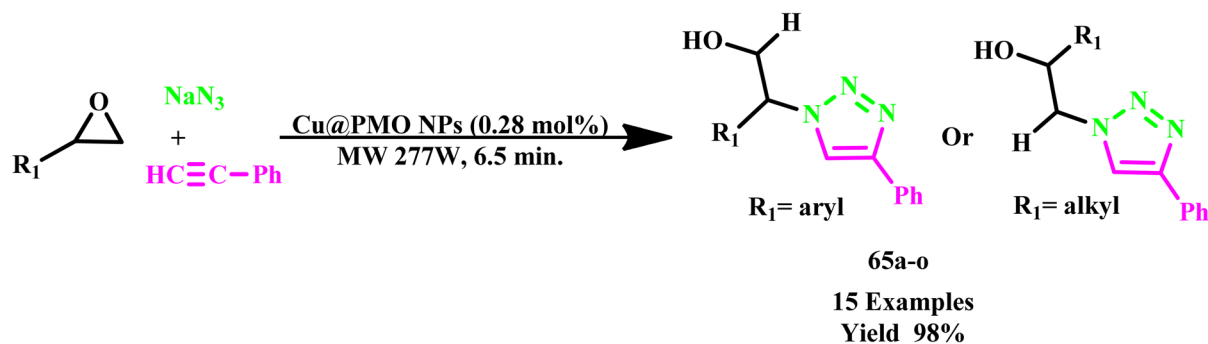
Similarly, Sood *et al.* reported a quick and high-yielding method for 1,2,3-triazole functionalized polysulfone derivatives (72a–e) using microwave-assisted synthesis (Scheme 61). The ultimate characteristics (mechanical, thermal, proton

Scheme 52 Microwave-assisted synthesis of 3-formyl-indole clubbed 1,2,3-triazole derivatives (63a-g).<sup>99</sup>Scheme 53 Microwave-assisted synthetic route for 1H-phenanthro[9,10-d][1,2,3]triazole (64).<sup>100</sup>

conduction) of the functionalized polymer are determined by the degree of 1,2,3-triazole functionalization of the polymer and the chemical structure of the ring substituent. However, the proton conductivities of phosphoric acid-doped polysulfone carrying 4-heptyl-1,2,3-triazole were found to be greater than those of carrying 4-phenyl-1,2,3-triazole because the former possessed higher chain mobility and lower Tg.<sup>108</sup>

Further, in another report, a mild and flexible one-pot three-component process for [3 + 2]-cycloaddition for new imine 1,4-disubstituted 1,2,3-triazoles derivatives (73a-k) was developed by Souza and co-worker using propargylamine,  $\alpha$ -thio aldehyde, and organoazides under the MW-assisted technique (Scheme 62). This protocol offers several advantages compared to conventional methods, such as less reaction time, easy product recovery and mild reaction conditions.<sup>109</sup>





$R_1 = \text{Ph, } p\text{-CH}_3\text{C}_6\text{H}_4, \text{n-But-1,4-diyl, C}_4\text{H}_9, \text{C}_2\text{H}_5, \text{PhOCH}_2, (\text{CH}_3)_2\text{CHOCH}_2, \text{C}_2\text{H}_2\text{COOCH}_2, \text{Cl-CH}_2, \text{TsO-CH}_2, \text{n-Hex-1,6-diyl, n-Dec-1,10-diyl}$

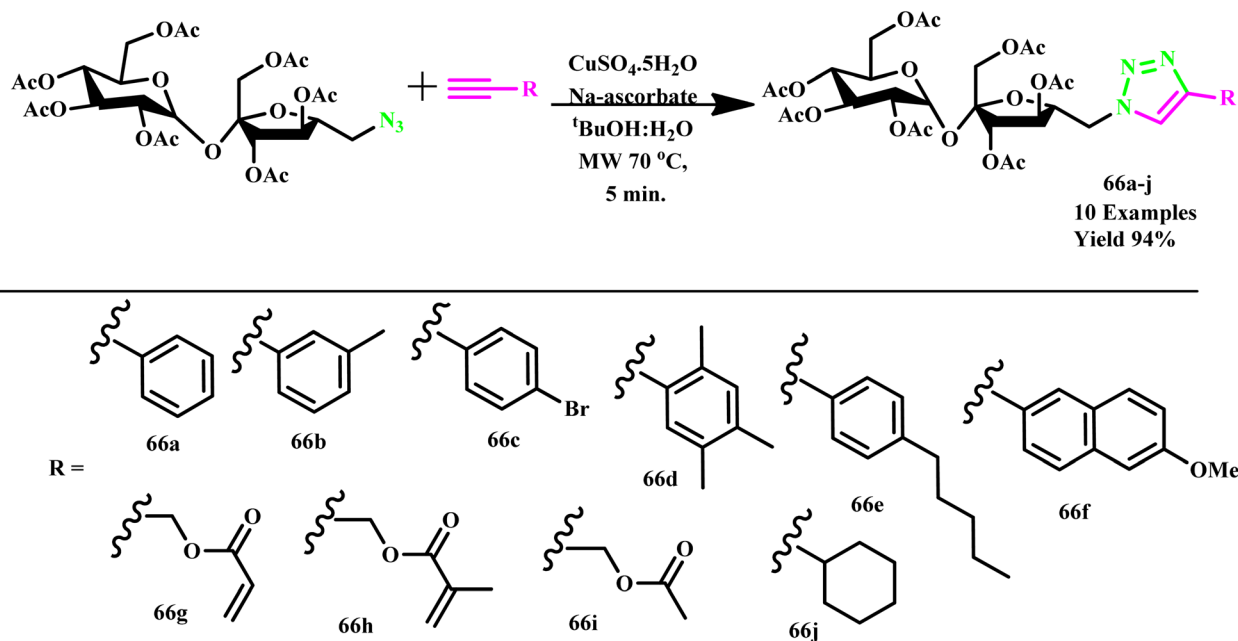
Scheme 54 Microwave-assisted synthetic route for beta-hydroxy-1,2,3-triazoles (65a-o).<sup>101</sup>

Similarly, Steenackers *et al.* developed a microwave-assisted one-pot approach for the generation of the 2-AIT framework (74a-z) (74aa-74ab) in which triazole moieties were attached to the 2*N*-position of the 2-AI ring through alkyl linkage (Scheme 63). The procedure combines a Dimroth-type rearrangement with an azide-alkyne cycloaddition reaction catalyzed by copper nanoparticles. Remarkably, the addition of a triazole moiety to their side chain of 2-aminoimidazoles with a lengthy 2*N*-alkyl chain (C8-C13) significantly increased their activity. The synthesized 2-amino-1*H*-imidazole/triazole conjugates exhibited high inhibitory action against the biofilms of *E. coli*, *S. typhimurium*, *S. aureus*, and *P. aeruginosa*, offering a lead structure for the further design and development of novel bio-film inhibitors.<sup>110</sup>

Using “click chemistry”, five mandipropamid analogues (75a-d) were synthesized and designed by Su and coworkers. A

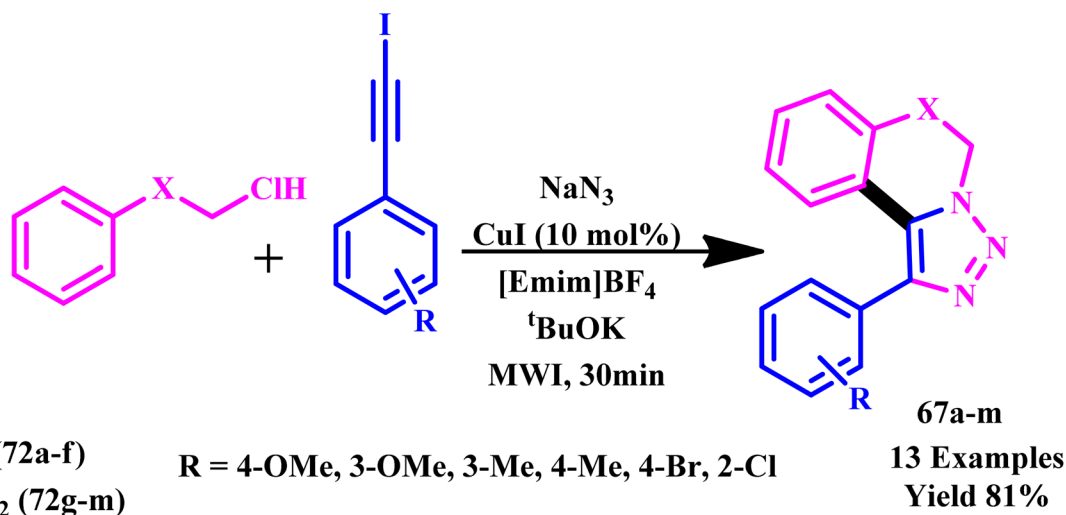
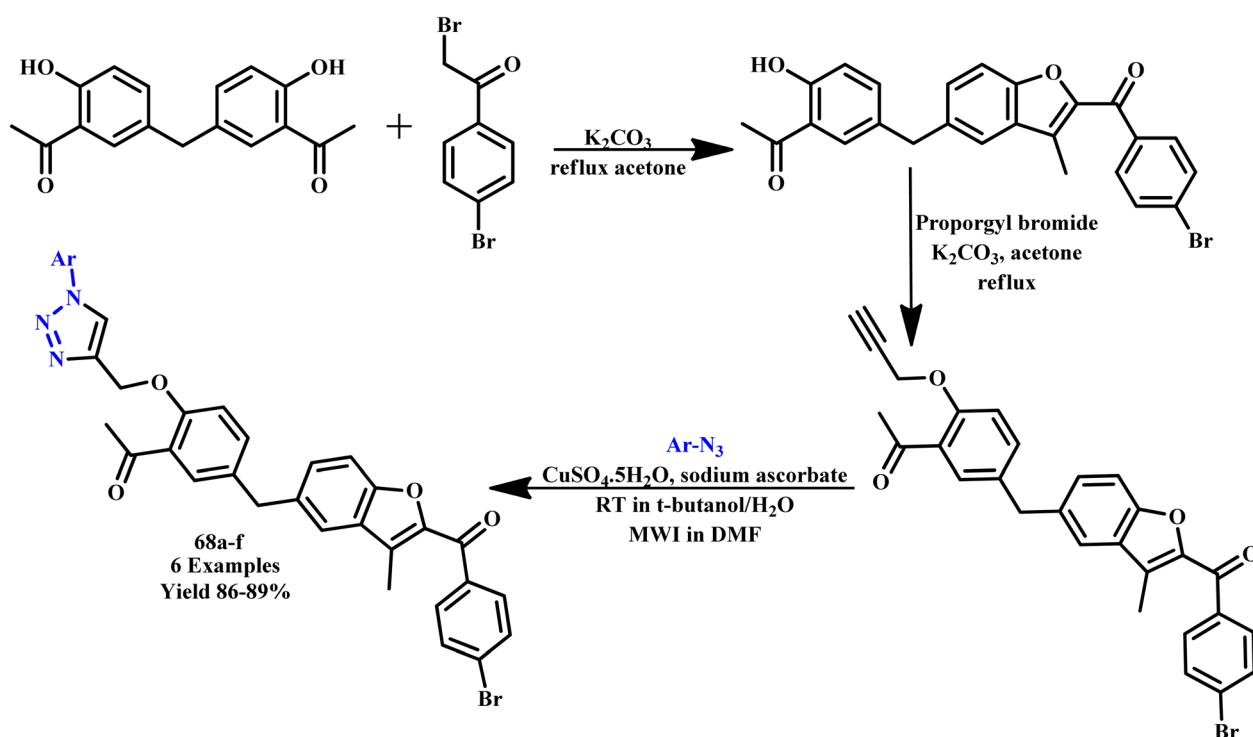
1,2,3-triazole functional group was replaced with a phenyl ring in mandipropamid (Scheme 64). According to the bioassay results, some of the reported compounds demonstrated a considerable amount of fungicidal activity. For example, *N*-(3,4-dimethoxyphenethyl)-2-ethoxy-2-(1-(2,2,2-trifluoroethyl)-1*H*-1,2,3-triazol-4-yl)acetamide and *N*-(3,4-dimethoxyphenethyl)-2-allyloxy-2-(1-(2,2,2-trifluoroethyl)-1*H*-1,2,3-triazol-4-yl)acetamide showed moderate activity (31.0%) at 100  $\mu\text{g mL}^{-1}$  and moderate activity (38.5%) at 50  $\mu\text{g mL}^{-1}$  against *Brassica* and *B. berengeriana*.<sup>111</sup>

Similarly, under microwave-irradiation, N. Subhashini and his coworker synthesized novel pyrazole-based 1,2,3-triazole derivatives (76a-o) via a Huisgen click reaction from organic azides and 1-phenyl-3-[3-(prop-2-yn-1-yloxy)phenyl]-1*H*-pyrazole-4-carbaldehyde using the redox system  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ -sodium ascorbate (Scheme 65). It was found that compared to



Scheme 55 Microwave-assisted synthetic route for 1,2,3-triazole-sucrose derivatives (66a-j).<sup>102</sup>

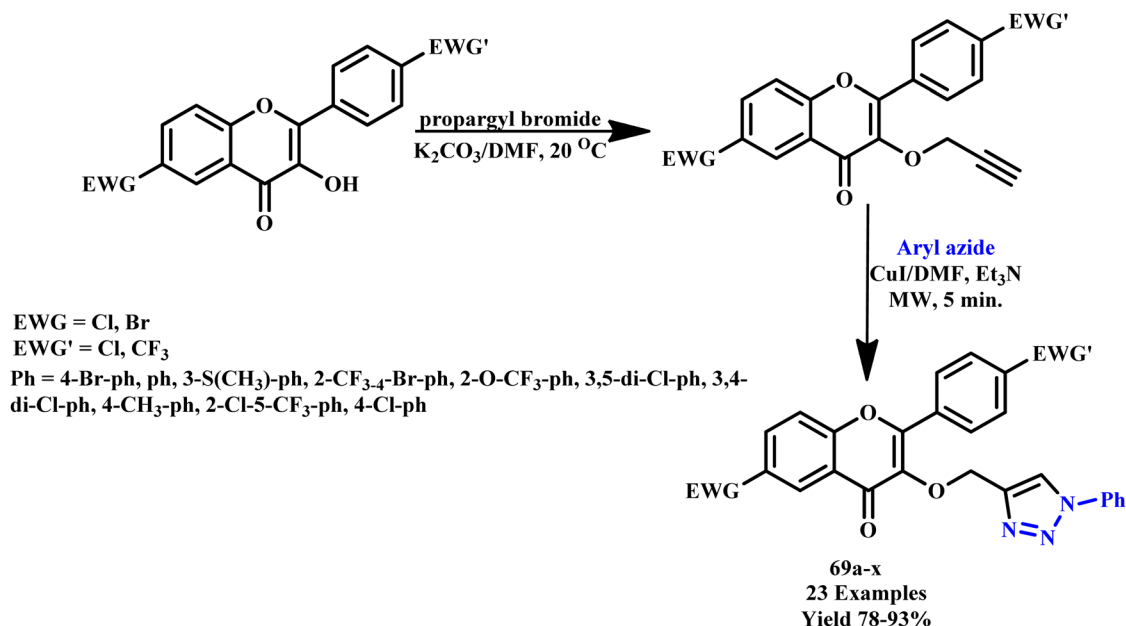
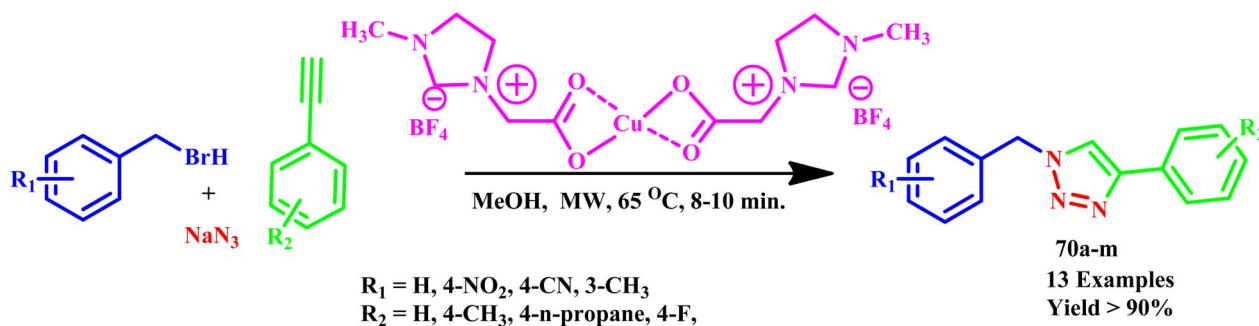
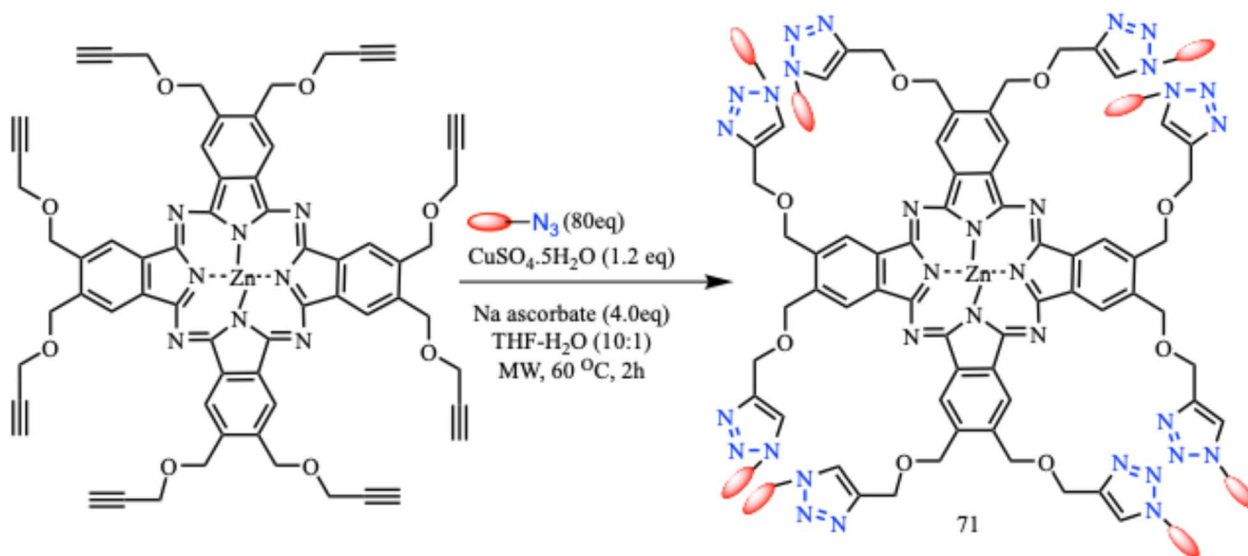
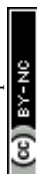


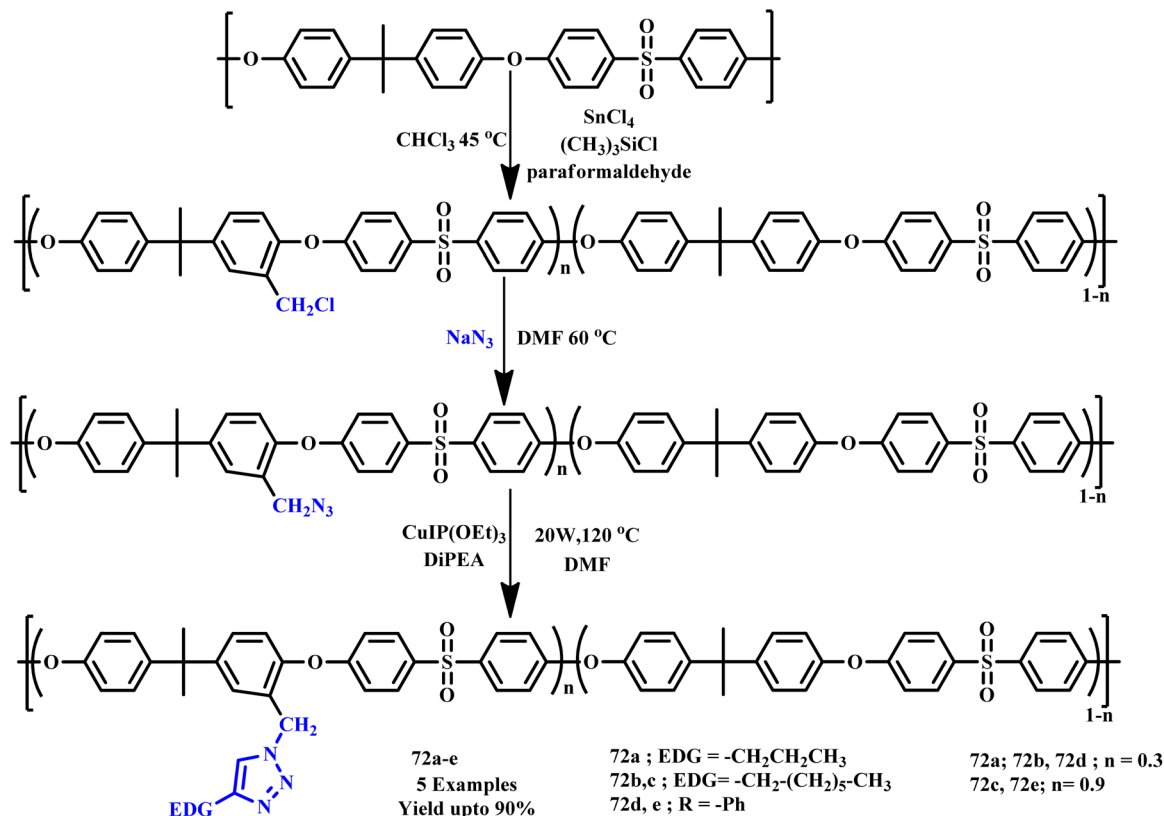
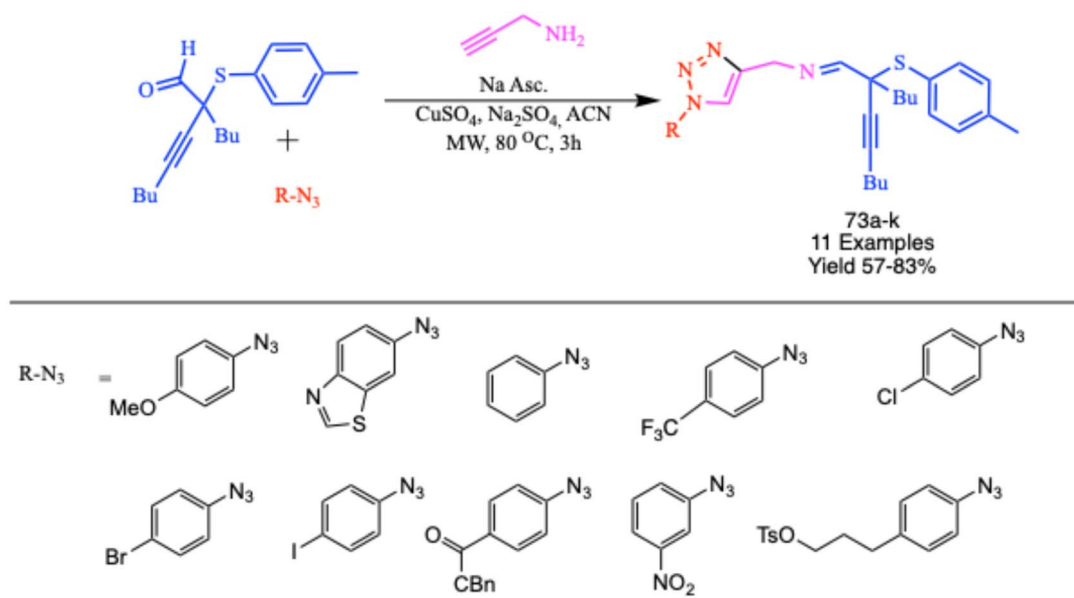
Scheme 56 Microwave-assisted synthetic route for fused benzo[e]1,2,3-triazoles (67a-m).<sup>103</sup>Scheme 57 Microwave-assisted synthesis of benzofuran-based 1,2,3-triazoles (68a-f).<sup>104</sup>

the conventional heating method (required 12–16 h at rt), the reported methodology required less time (4–6 minutes) to complete the reaction at 180 W and provide a better yield (up to 80–90%). Additionally, antimicrobial activity was tested on all obtained compounds, and it was found that 3-(3-([1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]-methoxy)phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde and 3-(3-([1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl]-methoxy)phenyl)-1-phenyl-1H-

pyrazole-4-carbaldehyde exhibited stronger activities than reference medication against pathogenic bacteria.<sup>112</sup>

BasappaVagish reported microwave irradiation-based synthesis of  $\alpha,\beta$ -unsaturated carbonyl-linked coumarin-triazole hybrid compounds (77a-e) (Scheme 66). The intermolecular interactions are quantified by Hirshfeld surface analysis, and crystal structure analysis demonstrates that the C–O $\cdots$  $\pi$ , C–H $\cdots$  $\pi$  and  $\pi$ – $\pi$  stabilize the crystal structure. Additionally, coumarin-triazole hybrid target compounds were tested in an *in*

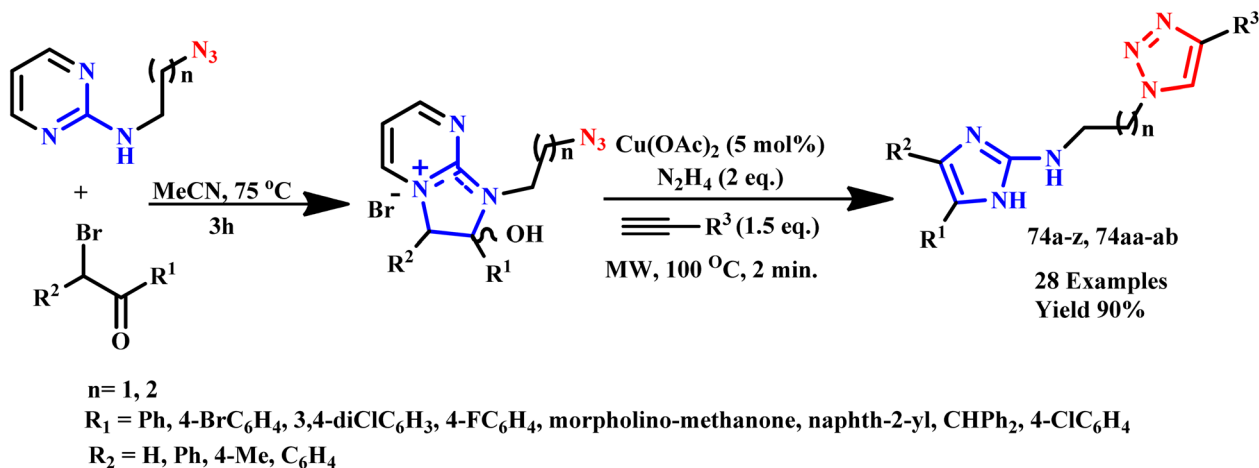
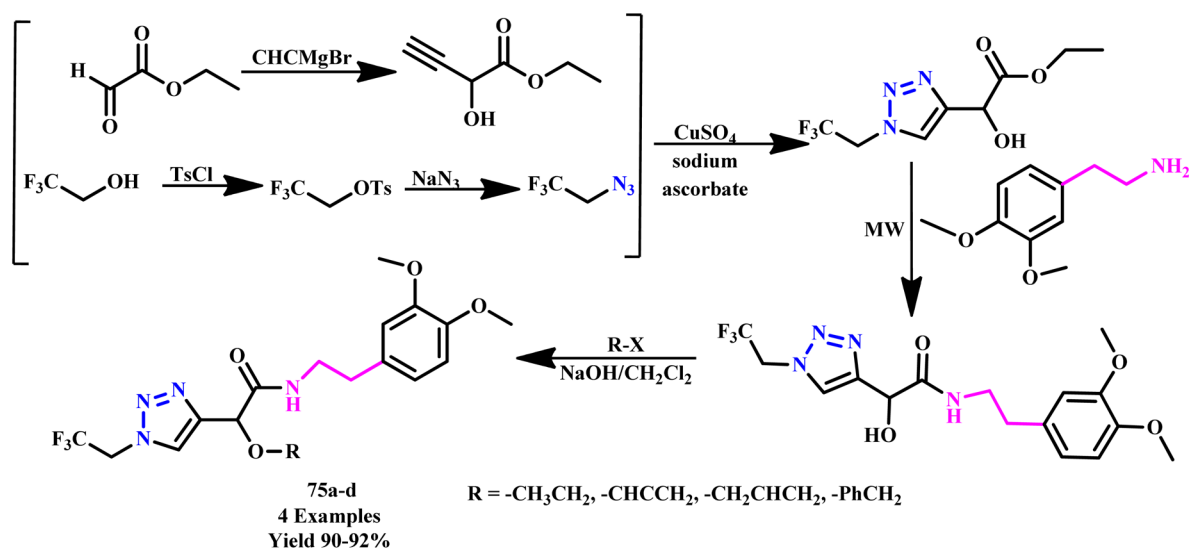
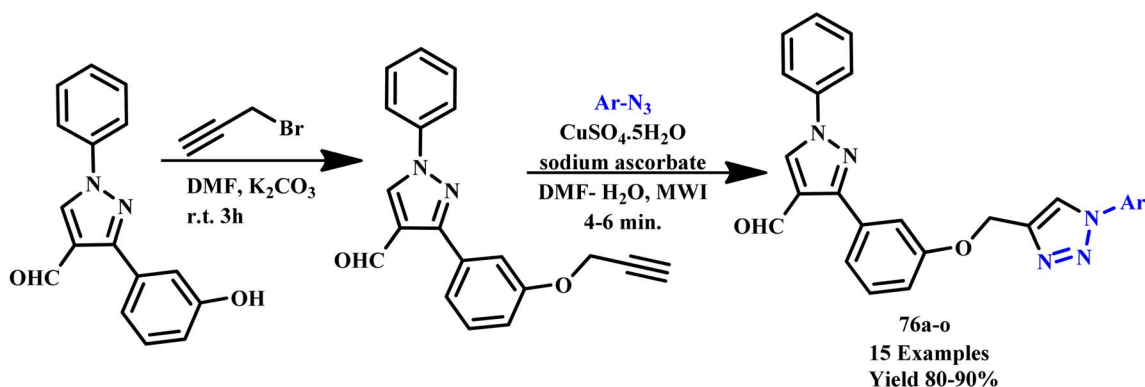
Scheme 58 Microwave-assisted synthesis of 1,2,3-triazole derivatives (69a-x).<sup>105</sup>Scheme 59 Microwave-assisted synthetic route of 1,4-disubstituted 1,2,3-triazoles (70a-m).<sup>106</sup>Scheme 60 Microwave-assisted synthesis and deprotection of ZnPc-peptide conjugates (71).<sup>107</sup>

Scheme 61 Microwave-assisted synthesis of 1,2,3-triazole functionalized polysulfones (72a–e).<sup>108</sup>Scheme 62 Microwave-assisted synthesis of 1,2,3-triazoles (73a–k).<sup>109</sup>

*vitro* study for their anticancer efficacy against the PC-3 and DU-145 cell lines. The outcome demonstrates that 3-(3-(1-(4-bromophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-oxoprop-1-en-1-yl)-4-chloro-2*H*-chromen-2-one was found to be more effective against DU-145 and PC-3 cell lines with IC<sub>50</sub> values of 9.845 ±

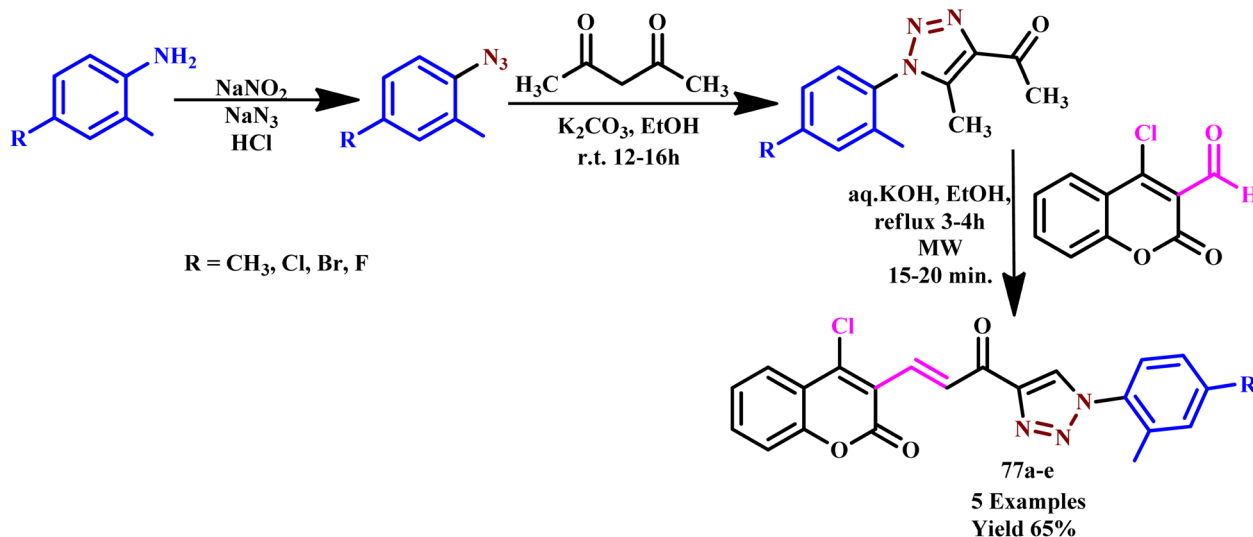
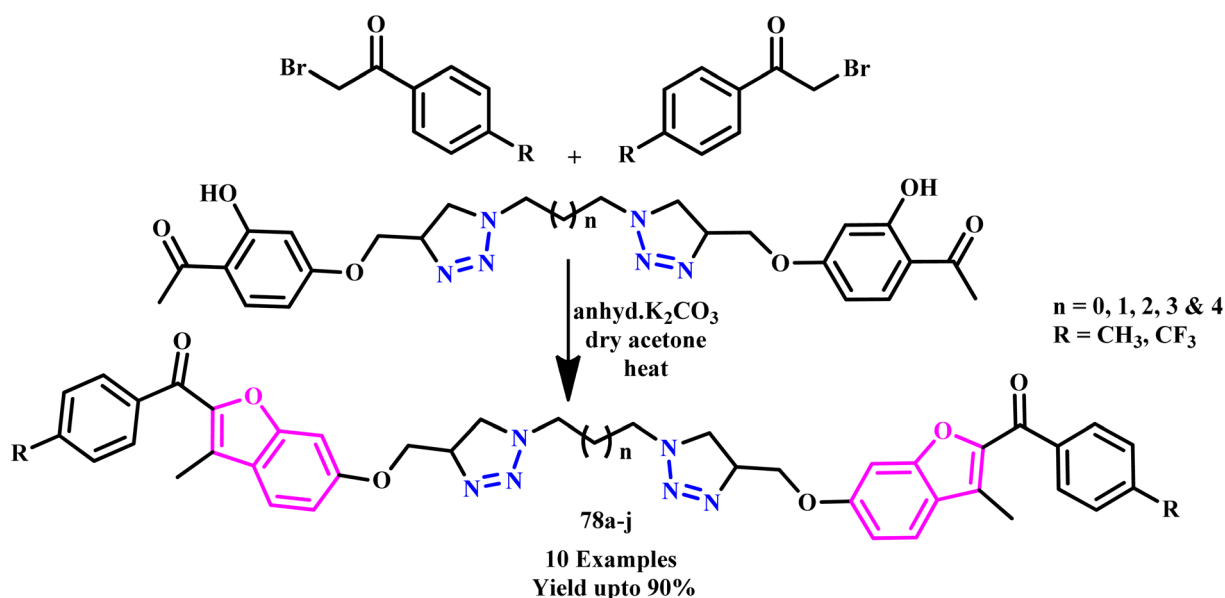
0.6 μM and 10.538 ± 0.3, respectively, with minimum toxicity at 10 μM. To obtain the desired product, conventional heating requires 3–4 h with 70% yield, while microwave-assisted protocol requires lesser reaction time (25–30 minutes) and 65% yield.<sup>113</sup>



Scheme 63 Microwave-assisted synthesis of the 2-AIT framework (74a–z) (74aa–74ab).<sup>110</sup>Scheme 64 Microwave-assisted synthesis of mandipropamid analogues (75a–d).<sup>111</sup>

$\text{Ar} = \text{phenyl, p-tolyl, m-toyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-nitrophenyl, 4-nitrophenyl, 4-carboxyphenyl, 4-methoxy-2-nitrophenyl, 2-methoxy-4-nitrophenyl, 4-acetylphenyl, 4-benzoylphenyl}$

Scheme 65 Microwave-assisted synthesis of pyrazole-based 1,2,3-triazoles (76a–o).<sup>112</sup>

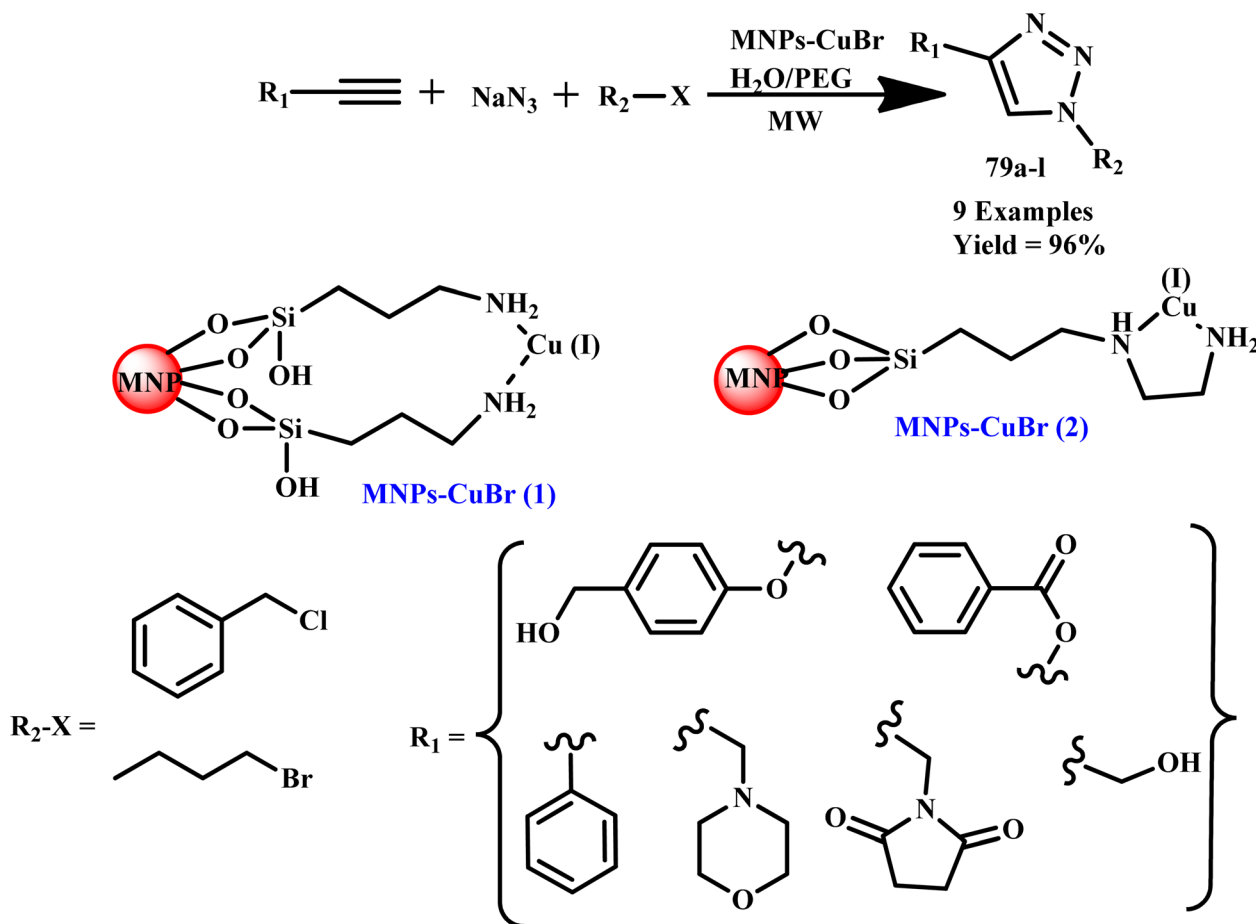
Scheme 66 Microwave-assisted synthesis of coumarin-1,2,3-triazole conjugates (77a-e).<sup>113</sup>Scheme 67 Microwave-assisted synthesis of (6,6'-(1,1'-(propane-1,3-diyl)bis(1H-1,2,3-triazole-4,1-diyl)bis(methylene)bis(oxy)(3-methyl-benzofuran-6,2-diyl)bis(4-substituted phenylmethanone))) (78a-j).<sup>114</sup>

Vani *et al.* used both conventional and MW irradiation techniques for the synthesis of dimers of 1,2,3-triazole-benzofuran bearing alkyl spacer derivatives (78a-j) via intermediate bis-1,2,3-triazole-carrying alkyl spacer compounds under quick reaction times and mild reaction conditions (Scheme 67). All the synthesized compounds were evaluated for their antioxidant and antimicrobial properties. Compound 78b exhibits strong antibacterial action against Gram-positive bacteria, while compound 78j demonstrated strong antioxidant activity using the DPPH technique. It was observed that in the microwave, the reaction required only 5–7 minutes at 180 W with a good yield compared to the conventional method (7–10 h, 49–59 yields %).<sup>114</sup>

A highly active, easily recoverable synthesis of 1,2,3-triazole derivatives (79a-l) was reported by Xiong and Cai by employing a one-pot multi-component copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction in H<sub>2</sub>O. The terminal alkynes readily interacted with benzyl/alkyl azides produced *in situ* from corresponding sodium azide and primary halides under the MW irradiation conditions (MW, 480 W). In comparison to standard methods, microwave irradiation significantly reduces the reaction time while simultaneously improving yields up to 96% and the purity of 1,2,3-triazoles (Scheme 68).<sup>115</sup>

*In situ* generated aryl azides through the reaction of sodium azide and aryl diazonium silica sulfates, followed by coupling with a terminal alkyne in the presence of copper catalyst, were



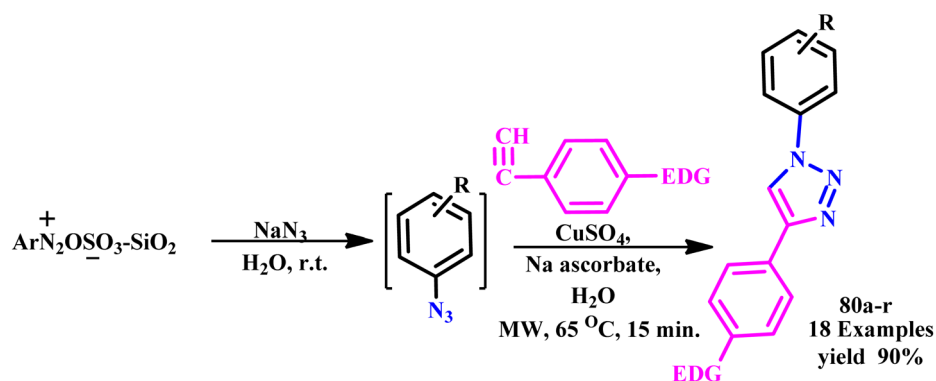


Scheme 68 Microwave-assisted one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles (79a–l) using the MNPs–CuBr catalyst.<sup>115</sup>

explored in the context of microwave-assisted click chemistry synthesis of 1,4-disubstituted 1,2,3-triazoles (80a–r) by Zarei and his coworker (Scheme 69). It was reported that without the need for additional ligands, these reactions were carried out in water under mild, heterogeneous circumstances. It was found that all the compounds were synthesized within 15 minutes at

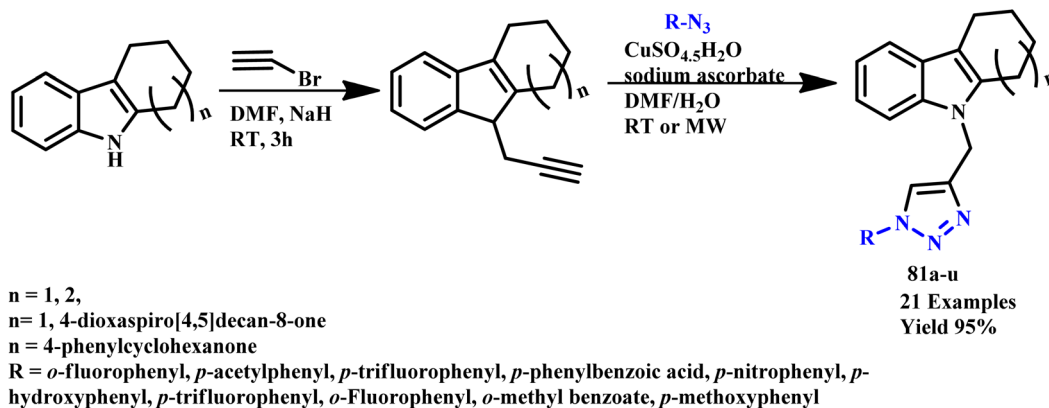
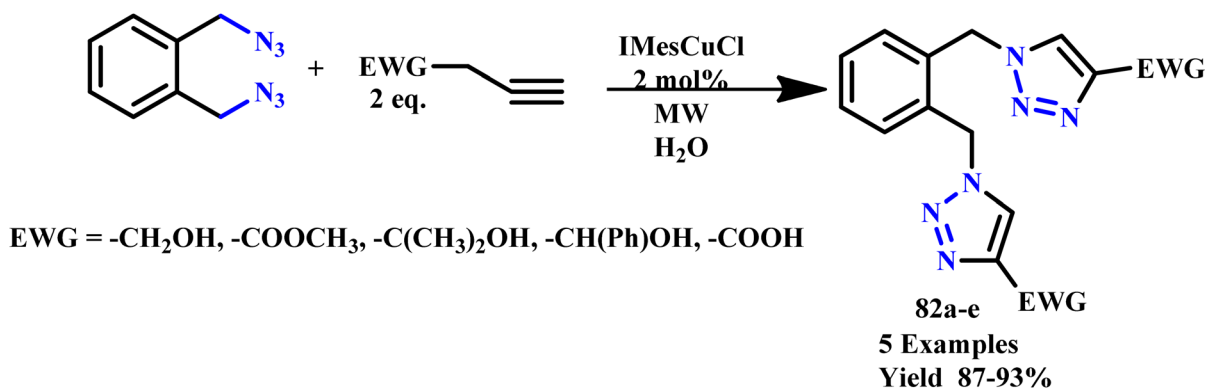
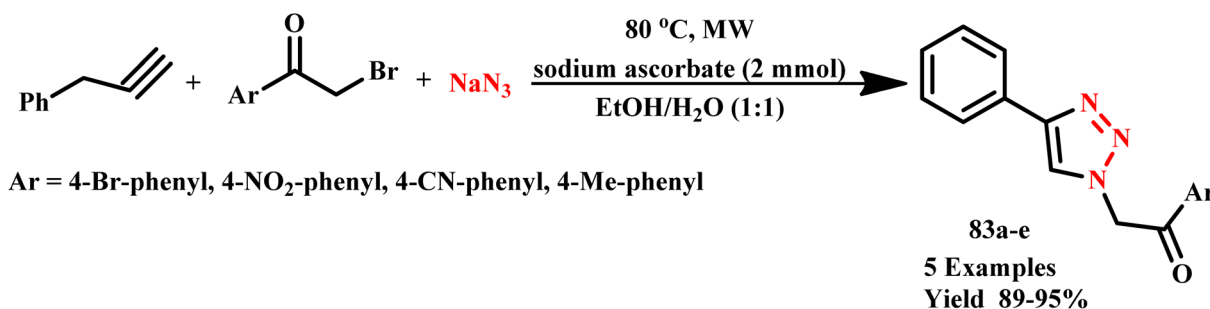
65 °C in a microwave-assisted process with 90% yield, while the same synthesis was carried out using the traditional method for 1–6 hours at room temperature to 70 °C with 76–86% yield.<sup>116</sup>

Ashok *et al.* developed a series of *N*-substituted 1,2,3-triazolylmethyl indole derivatives using MW irradiation to improve reaction efficiency. This synthesis involved the *N*-



Scheme 69 MW-assisted synthesis of 1,4-disubstituted 1,2,3-triazoles (80a–l).<sup>116</sup>



Scheme 70 MW-assisted synthesis of substituted 1,2,3-triazolylmethyl indole derivatives (**81a–u**).<sup>117</sup>Scheme 71 MW-assisted synthesis of 1,4-disubstituted bis-1H-1,2,3-triazoles (**82a–e**) using the NHC–Cu catalyst.<sup>118</sup>Scheme 72 MW-assisted synthesis of 1,4-disubstituted 1H-1,2,3-triazoles (**83a–e**) using NiO/Cu<sub>2</sub>O nanocomposite catalyst.<sup>119</sup>

alkylation of tetrahydro-1H-carbazoles, followed by a copper-catalyzed Huisgen [3 + 2] cycloaddition with various aromatic azides using copper sulfate and sodium ascorbate as catalysts (Scheme 70). MW irradiation significantly enhanced yields (72–96%) and reduced reaction times compared to conventional heating (64–94%) showing the efficiency of the method in promoting cycloaddition reaction. Characterization of all new compounds was completed through <sup>1</sup>HNMR and <sup>13</sup>CNMR, mass, and IR spectroscopy and biological evaluation, revealing notable antimicrobial, antioxidant and anticancer properties. Molecular docking studies further confirmed that these

compounds effectively fit into the active sites of caspase-3 and 17-beta-hydroxy steroid dehydrogenase type 1, suggesting their potential as bioactive agents.<sup>117</sup>

Mitchell *et al.* developed an efficient synthesis of 1,4-disubstituted bis-1H-1,2,3-triazoles using an NHC–Cu catalyst under MW conditions, achieving yields between 87% and 93% (Scheme 71). This protocol offers the advantages of high yields and shorter reaction times, where conventional heating in water requires a longer reaction time and low yield, which shows the time-saving potential of MW-assisted synthesis.<sup>118</sup>

Table 2 Comparative analysis of microwave-assisted 1,2,3-triazole synthesis results with conventional methods

| Entry | Structure | Name                                                                        | Conventional method |           |           | Microwave method |            |           | Ref. |
|-------|-----------|-----------------------------------------------------------------------------|---------------------|-----------|-----------|------------------|------------|-----------|------|
|       |           |                                                                             | Time (h)            | Temp (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 1     |           | Imidazole linked 1,2,3-triazole hybrid compounds                            | 4–5                 | 80        | 60–64     | 3–5              | 180 W      | 90–95     | 65   |
| 2     |           | Substituted 1,2,3-triazoles                                                 | 6–7                 | 200       | 28        | 6–7 hours        | 200        | 55–99     | 66   |
| 3     |           | 1,2,3-Triazole derivative                                                   | 3                   | rt        | 86        | 1                | 300 W      | 93        | 67   |
| 4     |           | Silicon-based multidentate triazole scaffold                                | 16                  | 25        | 71–92     | 21               | 60         | 86–98     | 68   |
| 5     |           | 1,2,3-Triazole-based pyrazole aldehydes and their benzimidazole derivatives | 5–8                 | 100       | 55–65     | 7–9              | 300 W      | 77–89     | 69   |
| 6     |           | Fused 1,2,3-triazoles                                                       | 20–24               | 100–140   | 47        | 30–40            | 150        | 88        | 70   |
| 7     |           | Acridone-based 1,2,3-triazole hybrid derivatives                            | 10                  | rt        | 60–75     | 10               | 40–100     | 65–88     | 71   |



Table 2 (Contd.)

| Entry | Structure | Name                                                                                                        | Conventional method |              |           | Microwave method |            |           | Ref. |
|-------|-----------|-------------------------------------------------------------------------------------------------------------|---------------------|--------------|-----------|------------------|------------|-----------|------|
|       |           |                                                                                                             | Time (h)            | Temp (°C)    | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 8     |           | 1-(5-Methyl-1-aryl-1H-1,2,3-triazol-4-yl)ethanone O-((1-aryl-1H-1,2,3-triazol-4-yl)methyl) oxime derivative | 8                   | 80           | 56        | 12               | 130 W      | 92        | 9    |
| 9     |           | 1-Monosubstituted 1,2,3-triazole derivative                                                                 | 12                  | 80           | 82        | 15               | 80         | 89        | 72   |
| 10    |           | <i>p</i> -Tolyloxyquinoline-triazole hybrid derivatives                                                     | 8–10                | rt           | 75        | 5–6              | 180 W      | 93        | 4    |
| 11    |           | <i>N</i> -bis-1,2,3-triazolo-linked-1,5-benzodiazepin-2-one (BZD) derivative                                | 24                  | rt or reflux | 30–45     | 6–7              | 400 W      | 67–92     | 73   |
| 12    |           | 1,2,4-Oxadiazol-5-ylmethyl-1,2,3-triazole derivatives                                                       | 16                  | 65           | 73        | 2.5              | 65         | 75–99     | 64   |
| 13    |           | 1,4-Disubstituted 1,2,3-triazole derivatives                                                                | 6–12                | 50–60        | 67        | 12               | 120        | 98        | 74   |
| 14    |           | Acridone-derived 1,2,3-triazole derivatives                                                                 | 4                   | 80           | 48–62     | 10               | 200 W      | 75–90     | 75   |
| 15    |           | 1,4-Disubstituted 1,2,3-triazole derivative                                                                 | 5                   | 50           | —         | 6                | 70         | 98        | 76   |
| 16    |           | 1,4-Disubstituted 1,2,3-triazole derivative                                                                 | —                   | —            | —         | 10–15            | 125        | 93        | 77   |

Table 2 (Contd.)

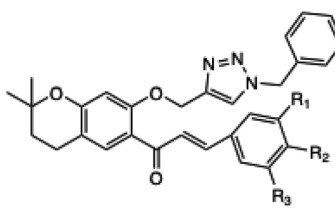
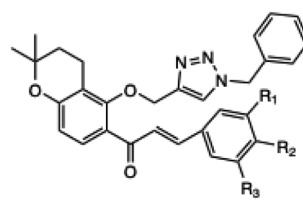
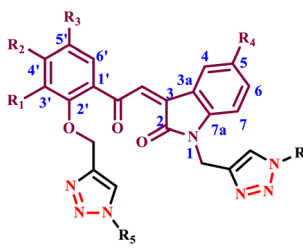
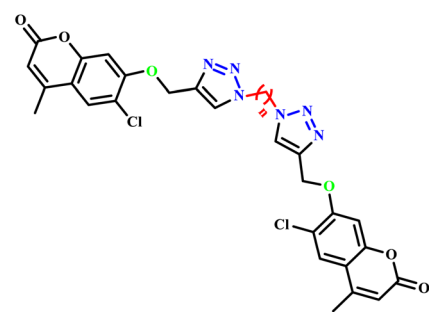
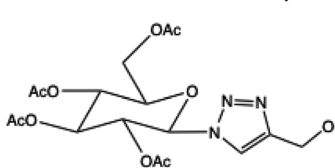
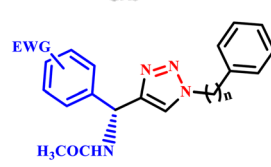
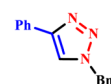
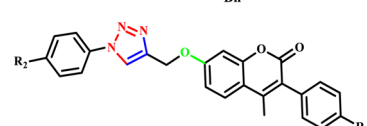
| Entry | Structure                                                                                                                                                                 | Name                                                                                                                                                                                                                             | Conventional method |           |           | Microwave method |            |           | Ref. |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------|-----------|------------------|------------|-----------|------|
|       |                                                                                                                                                                           |                                                                                                                                                                                                                                  | Time (h)            | Temp (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 17    | <br>or  | 1-[7-(1-Benzyl-1 <i>H</i> -[1,2,3] triazol-4-yl-methoxy)-2,2-dimethyl-chroman-6-yl]-3-aryl-2-propen-1-ones and 1-[5-(1-benzyl-1 <i>H</i> -[1,2,3] triazol-4-ylmethoxy)-2,2-dimethylchroman-6-yl]-3-aryl-propen-1-ones derivative | 24–26               | rt        | 30–66     | 8–15             | 180 W      | 85–94     | 78   |
| 18    |                                                                                         | 2-Indolinone-based bis-1,2,3-triazole derivatives                                                                                                                                                                                | 8–11 h              | 80        | 59–70     | 3–5              | 180 W      | 85–93     | 79   |
| 19    |                                                                                        | Coumarin-1,2,3-triazole hybrids                                                                                                                                                                                                  | 24                  | 80        | 43–52     | 10               | 180 W      | 79–86     | 80   |
| 20    |                                                                                        | 1,2,3-Triazole derivative                                                                                                                                                                                                        | —                   | —         | —         | 120              | 100        | 92        | 81   |
| 21    |                                                                                        | $\alpha$ -[4-(1-substituted)-1,2,3-triazol-4-yl]-benzylacetamide derivative                                                                                                                                                      | 2                   | rt        | —         | 10               | 125        | 92        | 82   |
| 22    |                                                                                        | 1,2,3-Triazole derivative                                                                                                                                                                                                        | —                   | —         | —         | 15               | 90         | 98        | 83   |
| 23    |                                                                                        | Coumarin-based 1,4-disubstituted 1,2,3-triazole derivatives                                                                                                                                                                      | 4–6                 | —         | 68–79     | 5–8              |            | 80–90     | 84   |



Table 2 (Contd.)

| Entry | Structure | Name                                                                                                                                             | Conventional method |           |           | Microwave method |            |           | Ref. |
|-------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-----------|-----------|------------------|------------|-----------|------|
|       |           |                                                                                                                                                  | Time (h)            | Temp (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 24    |           | 1,4-Dihydrochromene triazoles                                                                                                                    | 2.5                 | 80        | 86        | 20–55            | 80         | 83        | 85   |
| 25    |           | 1,2,3-Triazole 10-homo-30-isoazannucleoside derivative                                                                                           | 22                  | 70        | 70        | 30               | 70         | 92        | 87   |
| 26    |           | 4-Aryl-NH-1,2,3-triazole derivative                                                                                                              | 2–3                 | 130       | 91        | 5                | 130        | 94        | 88   |
| 27    |           | Triazole-linked amino acid-glucoside conjugates                                                                                                  |                     |           |           | 14               | 55         | 97        | 89   |
| 28    |           | Arylating 1,4-disubstituted 1,2,3-triazoles                                                                                                      | 24                  | Reflux    | 58        | 15               | 250        | 99        | 90   |
| 29    |           | 1,4-Disubstituted 1,2,3-triazole-linked glycodendrimers derivative                                                                               |                     |           |           | 20               | 80         | 99        | 91   |
| 30    |           | ( <i>E</i> )- <i>N'</i> -((1,3-diphenyl-1 <i>H</i> -pyrazol-4-yl)methylene)-3-(4-phenyl-1 <i>H</i> -1,2,3-triazol-1-yl)benzohydrazide derivative | 1–2                 | 80–100    | 65–80     | 4–6              | 300 W      | 88–98     | 92   |
| 31    |           | 1,2,3-Triazoles bearing isoxazole ether derivative                                                                                               | 6–10                | 50        | 45–84     | 10               | 50         | 80–95     | 93   |





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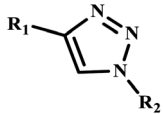
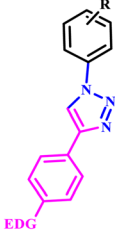
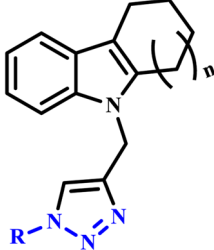
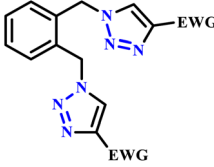
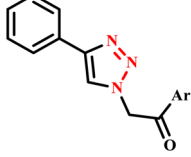
| Entry                                                                                      | Structure | Name                                                    | Conventional method |           |           | Microwave method |            |           | Ref. |
|--------------------------------------------------------------------------------------------|-----------|---------------------------------------------------------|---------------------|-----------|-----------|------------------|------------|-----------|------|
|                                                                                            |           |                                                         | Time (h)            | Temp (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 32                                                                                         | —         | <i>N,N</i> -metal-binding ligands into peptoid oligomer | 15–72               | rt        | —         | 35               | 60         | —         | 94   |
| 33                                                                                         |           | NH-1,2,3-triazoloimines                                 | 10 days             | rt        | 85        | 10               | 100        | 92        | 95   |
| 34                                                                                         |           | Pyridyl-1,2,3-triazole derivative                       | —                   | —         | —         | 12               | 160        | —         | 97   |
| R = 2-, 3-, 4-, 3,5-disubstituted alkyl, EDG, EWG                                          |           |                                                         |                     |           |           |                  |            |           |      |
| 35                                                                                         |           | 1,4-Dibstituted-1,2,3-triazole derivatives              | —                   | —         | —         | 60–120           | 45–80      | 55–98     | 98   |
| R1/R2 = Ph/PhCH2, Ph/CH2CO2Me, n-Bu/PhCH2, Ph/CH2CO2Bn, Ph/2-I-C6H4CH2, Ph/n-Bu, Ph/sec-Bu |           |                                                         |                     |           |           |                  |            |           |      |
| 36                                                                                         |           | 3-Formyl-indole clubbed 1,2,3-triazole derivatives      | —                   | —         | —         | 15               | 70         | 92–93     | 99   |
| 37                                                                                         |           | 1 <i>H</i> -phenanthro[9,10- <i>d</i> ][1,2,3]triazole  | —                   | —         | —         | 45 seconds       | 700 W      | 62        | 100  |
| 38                                                                                         |           | $\beta$ -Hydroxy-1,2,3-triazole derivative              | —                   | —         | —         | 6                | 277 W      | 97.54     | 101  |
| 39                                                                                         |           | 1,2,3-Triazole-sucrose derivatives                      | 3                   | 70        | 91        | 5                | 70         | 82–94     | 102  |
| 40                                                                                         |           | Fused 1,2,3-triazole                                    | 20                  | 140       | 45        | 30               | 150        | 81        | 103  |
| 41                                                                                         |           | Benzofuran-based 1,2,3-triazole derivatives             | 23–24               | rt        | 62–71     | 6–8              | 180 W      | 82–89     | 104  |



Table 2 (Contd.)

| Entry | Structure | Name                                                       | Conventional method |           |           | Microwave method |            |           | Ref. |
|-------|-----------|------------------------------------------------------------|---------------------|-----------|-----------|------------------|------------|-----------|------|
|       |           |                                                            | Time (h)            | Temp (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 42    |           | 1,2,3-Triazole linked flavonol hybrids                     | 12–24               | 110       | 55–65     | 3–5              | 250 W      | 78–93     | 105  |
| 43    |           | 1,4-Disubstituted 1,2,3-triazoles                          | 4                   | Reflux    | 80        | 8–10             | 65         | 95        | 106  |
| 44    |           | Triazole-linked phthalocyanine-peptide derivative          | 20                  | rt        |           | 120              | 60         | 86        | 107  |
| 45    |           | 1,2,3-Triazole-functionalized polysulfone                  | —                   | —         | —         | 10               | 120        | >80       | 108  |
| 46    |           | Imine-1,4-disubstituted 1,2,3-triazoles derivative         | 10                  |           |           | 120–180          | 80         | 57–83     | 109  |
| 47    |           | 2-Amino-1H-imidazole/triazole conjugates                   | 24                  | rt        | 24        | 2                | 100        | 90        | 110  |
| 48    |           | 1,2,3-Triazole derivative                                  | 10                  | 130–140   | 25        | 30               | 125        | 92        | 111  |
| 49    |           | Pyrazole-based 1,2,3-triazole derivatives                  | 12–18               | rt        | 65–73     | 4–6              | 180 W      | 80–90     | 112  |
| 50    |           | Coumarin-triazole hybrid derivative                        | 3–4                 | rt        | 62–70     | 15–30            | 160–320 W  | 58–65     | 113  |
| 51    |           | 1,2,3-Triazole-benzofuran bearing alkyl spacer derivatives | 7–10                | Refluxed  | 49–59     | 5–7              | 180 W      | 87–96     | 114  |

Table 2 (Contd.)

| Entry | Structure                                                                           | Name                                        | Conventional method |           |           | Microwave method |            |           | Ref. |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------|---------------------|-----------|-----------|------------------|------------|-----------|------|
|       |                                                                                     |                                             | Time (h)            | Temp (°C) | Yield (%) | Time (min)       | Temp. (°C) | Yield (%) |      |
| 52    |    | 1,4-Disubstituted 1,2,3-triazole derivative | —                   | —         | —         | 15–28            | 480 W      | 89–96     | 115  |
| 53    |    | 1,4-Disubstituted 1,2,3-triazoles           | 6                   | rt        | 78        | 15               | 65         | 90        | 116  |
| 54    |    | N-substituted 1,2,3-triazolylmethyl indole  | 8–10                | rt        | 64–94     | 6                | 100 W      | 72–96     | 117  |
| 55    |   | 1,4-Disubstituted bis-1H-1,2,3-triazoles    | 12–24               | rt        | 56–98     | 15               | 80         | 59–98     | 118  |
| 56    |  | 1,4-Disubstituted 1,2,3-triazoles           | 24                  | 80        | 62        | 10               | 80         | 94        | 119  |

In a recent study, NiO/Cu<sub>2</sub>O nanocomposites (NCs) were employed as heterogeneous nanocatalysts Ni–CuAAC to synthesize 1,4-disubstituted 1,2,3-triazoles with a high product yield under microwave irradiation (Scheme 72). The NiO/Cu<sub>2</sub>O NCs were prepared *via* coprecipitation of NiO nanoparticles onto a Cu<sub>2</sub>O surface generating a robust composite with enhanced catalytic capabilities. This catalyst facilitated reactions between benzoyl azides and phenylacetylene under optimized conditions in which NiO/Cu<sub>2</sub>O NCs demonstrated superior catalytic activity compared to Cu<sub>2</sub>O nanoparticles. Additionally, the use of an ethanol–water solvent system under microwave irradiation improved yields (89–95%) with simplified product separation.<sup>119</sup> A comparative analysis of microwave-assisted 1,2,3-triazoles synthesis with conventional methods is tabulated in Table 2.

## Conclusion

In conclusion, microwave synthesis has emerged as a transformative and environmentally friendly laboratory method for synthesizing various triazole derivatives. This technique boasts rapid reaction rates and remarkably short reaction times, typically ranging from few seconds to minutes. Such efficiency enhances yields and promotes superior atom economy in chemical processes. By minimizing hazards and demonstrating compatibility with a wide array of reactants, microwave synthesis ensures a safer pathway for synthesizing triazole derivatives. Its energy-efficient nature and scalability highlight its significant environmental advantages. Beyond these benefits, microwave synthesis breaks new ground in triazole synthetic chemistry by facilitating reactions that are traditionally difficult or unachievable with conventional heating.



methods. Thus, it represents a pivotal advancement in sustainable triazole synthesis, promising broader applications and innovations in the field.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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