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Nano-Catalytic Synthesis of 5 Substituted 1H Tetrazole Derivatives and Biological Applications

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Abstract: This review explores the innovative use of nano-catalysts in the synthesis of 5-substituted 1H-tetrazole derivatives, highlighting their significant biological applications. The novel methodologies discussed demonstrate enhanced efficiency and selectivity in the production of these compounds. Key findings include the optimization of reaction conditions and the discovery of new catalytic pathways that improve yield and reduce reaction time. The synthesized tetrazole derivatives exhibit strong potential as therapeutic agents due to their biological activity. This work provides a comprehensive overview of the state-of-the-art techniques in nano-catalytic synthesis, emphasizing their practical applications in medicinal chemistry and materials science.

Keywords: Nano-Catalyst, Tetrazole derivatives, 5-substituted.

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1. INTRODUCTION

Tetrazoles are artificial heterocyclic organic compounds that have one carbon atom and four nitrogen atoms arranged in a five-membered ring. They are among the stable heterocycles with the highest nitrogen concentration. Tetrazoles are classified into two more common categories according to the number of substituents (Figure 1): (i) the simplest parent tetrazoles, (ii) Tetrazoles that have been mono-, 2-, or 5-substituted, (iii) Tetrazoles that are di-substituted (1,5- or 2,5-disubstituted).

"J. A. Bladin created and described tetrazole for the first time in 1885 (1,2), marking a significant milestone in organic chemistry. His pioneering work, conducted on the campus of Uppsala University, laid the foundation for subsequent studies exploring tetrazole derivatives' diverse applications in pharmaceuticals, materials science, and other fields, as evidenced by numerous scholarly articles available on Google Scholar. Tetrazoles exhibit stability throughout an extensive pH range and demonstrate resistance to a variety of oxidizing and reducing agents (1). They function as ligands in coordination chemistry and are essential (2) as explosives within the field of material science (3) and serve as substitutes for carboxylic acids in medicinal chemistry (4). Because of the many nitrogen atoms in their structure, they function as flexible pharmacophores in medicinal chemistry. Among the drugs are those with tetrazole rings. Antimicrobial (5), antifungal (6), antiviral (7), analgesic (8), and anti-inflammatory (9).

In recent years, advancements in nanoscience and nanotechnology have brought about revolutionary changes in many sectors, such as biology, medicine, wellness, environmental protection, and catalysis (10,11). Utilizing nanotechnology to capitalize on catalytic processes is one of the most important research fields among them, considering its direct influence on human society and evolution (12,13). The name "Nano" comes from the Greek word "dwarf". Anything that is at least one magnitude smaller than 100 nm in nanotechnology and has a clear view of its limit is called a nanoparticle (NP)

(14). Applications for nanoscale materials are growing in frequency, including fuel conversion, pollution control, and chemical synthesis. Transition metal NPs are of particular interest in nearly every branch of research and industry (15,16). Depending on their size, shape, composition, aggregation, material origin, and similarity, nanocatalysts can be distinguished from one another. Among other factors, the structure and form of NPs have a significant influence in determining how dangerous they are to people and their surroundings (17,18). Because of their enormous catalytic activity, NPs are useful for chemical procedures in both industry and research (19,20). There are several different kinds of NPs, including metal/metal oxide, ceramic, semiconductor, carbon-based, and polymeric NPs (21-26), among the first uses of NPs in catalysis. Several substances and elements, including titanium dioxide, steel, aluminum, and silica, have been employed as nanoscale catalysts over the past decades (27,28). It has been successful in using nanocrystalline metal oxides as poisons and gasses of hazardous substances (29). The literature claims that changing a nanomaterial's size, texture, and composition can change its properties (30-33). The ability of the activity catalyst to be retrieved from the reaction media after the reaction is a critical component in determining its utility in practical applications. On a large scale, this problem poses serious environmental and financial challenges. Because of this, heterogeneous catalysts are much more varied and often used in industry than homogeneous catalysts (34,35). However, heterogeneous catalysts' lack of efficiency is their worst flaw, which is why developing catalysts with extremely high efficiencies is a top priority. In addition to organic modification, nanocatalysts have many other uses (36,37). Thermal decomposition, organic vapor synthesis, microwave irradiation, sol-gel process, non-sono and sonoelectrooxidation, chemical precipitation, the hydrothermal approach, the photochemical method, shine discharge plasma electrolysis, the antisolvent the process of the precipitation microwave radiation exposure, wet-chemical approach, and sonochemical strategy are among the many techniques utilized for producing these nanocatalysts (36-40). To grasp the significance of nanocatalysts, one can examine the information available on the (Web of Science) platform, covering the period from 2000 to 2022. The volume of publications has shown a consistent annual rise, with notable advancements emerging, particularly after 2010. This observation leads us to posit that the realm of nanotechnology exerts influence across various scientific domains, see (Figure 2). 5-replaced 1H-tetrazoles are among the most significant and fascinating of all the tetrazole classes due to their many applications in the field of medicinal chemistry. Thus, the most recent developments in the synthesis of 5-replaced 1H-tetrazoles will be the main subject of this study.

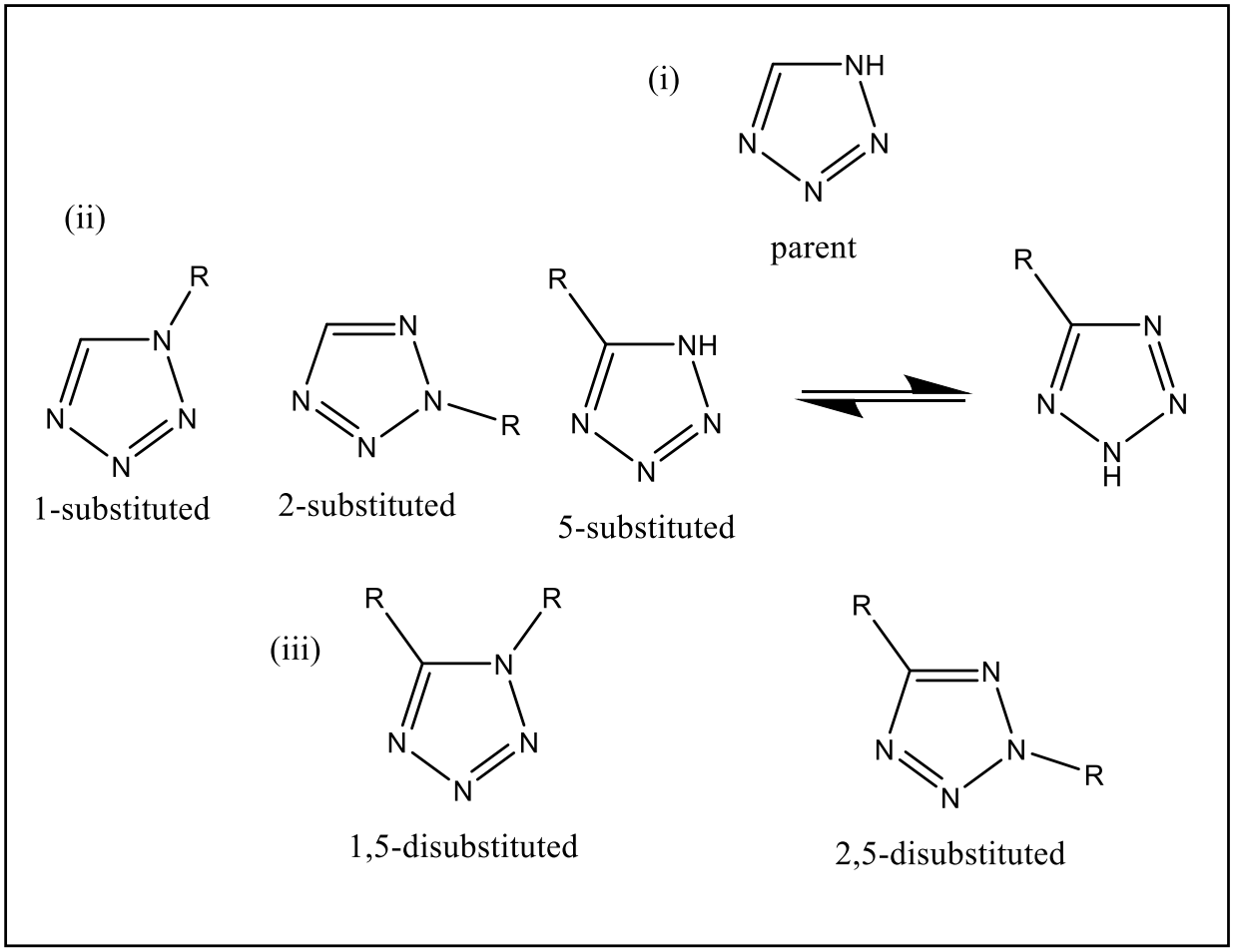


Figure 1: The classification of tetrazoles (37).

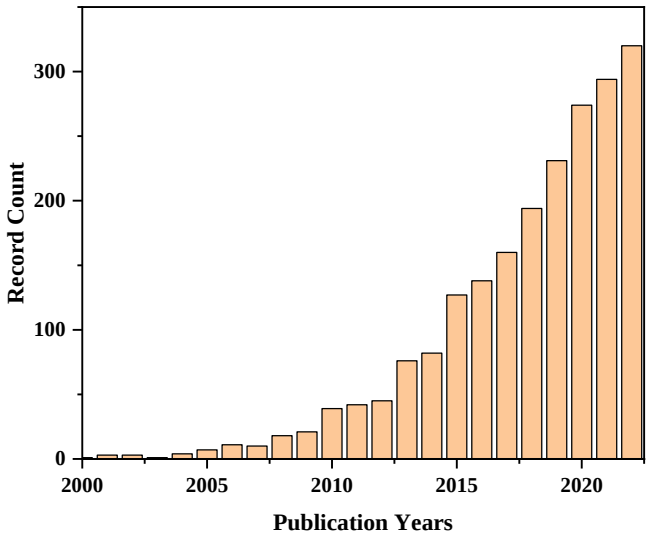
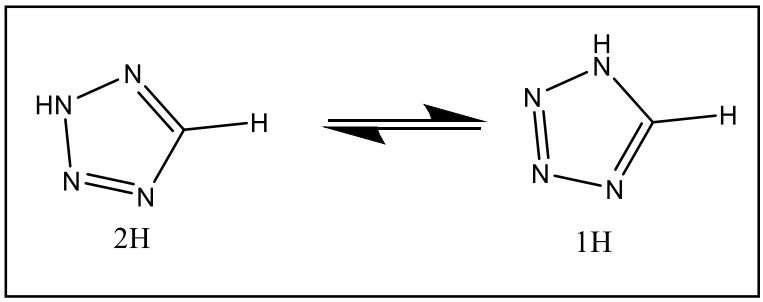


Figure 2: Publication vs. year record of published nanocatalysts.

2. THE FUNCTION OF 1H-TETRAZOLES WITH 5-SUBSTITUTES IN MEDICINAL CHEMISTRY

In medicinal chemistry, 1H-tetrazoles with five substitutes are frequently used as carboxylic acid bioisosteric substitutes or, more precisely, as carboxylic acid surrogates (41). Despite structural differences, neither of these functional groups exhibits comparable biological activity because of substantially related physiochemical characteristics (42). It is known that there are two tautomeric forms of 1H-tetrazoles with five substitutes with a free N-H bond: 1H- and 2H-tautomers in an approximately 1:1 ratio (Scheme 1) (43). Larsen, Liljebris, and coworkers (44) found that, as compared to utilizing the comparable carboxylate counterparts, adding a lipophilic tetrazole moiety to a range of PTB1B inhibitors dramatically enhanced Caco-2 cell permeability. The impact of substituting a 1H-tetrazole with five substitutes for a carboxylic acid in terms of pharmacodynamics is complex. It is impossible to forecast with any degree of accuracy whether the pharmacodynamics will rise, fall, or even vanish (45). A negative charge resonance in the tetrazole ring may raise or lower the interaction with a certain receptor, according to the electron configuration within a receptor site (46). The primary benefit of 1H-tetrazoles with five substitutes is that one of its nitrogen atoms can be glucuronidated, allowing both of its tautomers to act as platforms (47).



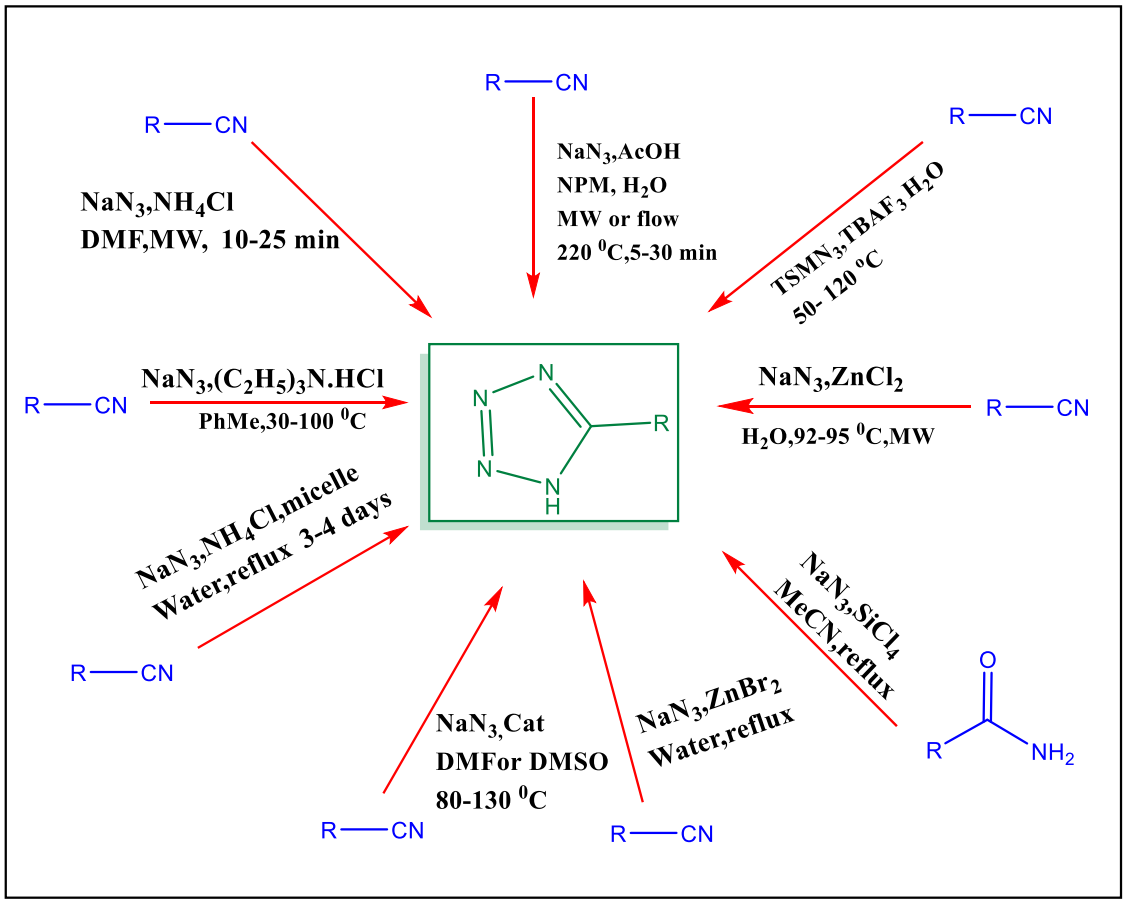
Scheme 1: The two tautomeric forms of 1H-tetrazoles with five substitutes (43).

3. DIFFERENT METHODS TO SYNTHESIZE TETRAZOLES WITH FIVE SUBSTITUTES

Tetrazoles with five substitutes Have been used in photography, organic chemistry, medicine, and weaponry (45). It is an important intermediate in the synthesis of organic compounds that is derived from tetrazole in organic chemistry. (Scheme 2) and (Table 1) show some indicated methods for producing these specific tetrazole derivatives. The majority of these methods are based on the condensation of a CN group plus an azide moiety. Tetrazoles with five substitutes can be synthesized by (I) Nitrile reaction with NaN_3 and NH_4Cl or $(C_2H_5)_3N.HCl$ in N, N-dimethylformamide (DMF) with microwave assistance (48), (II) Nitrile, and NaN_3 reacting using $(C_2H_5)_3N.HCl$ in toluene (49), (III) ammonium chloride, dodecyl trimethylammonium or hexadecyl trimethylammonium bromides, and nitrile condensation using water with NaN_3 (2), (IV) acetic acid and NaN_3 used to treat nitrile in N-methyl pyrrolidine-2-one (NMP) solution (50), (V) Trimethylsilyl azide ($TMSN_3$) and nitrile are reacted by tetrabutylammonium fluoride (TBAF) trihydrate (51), Microwave procedure for treating (NaN_3) in H_2O with nitrile and $ZnCl_2$ (52), (VII) amide, NaN_3, and HCl_3Si undergo MeCN condensation (53), (VIII) Under a reflux condition, zinc bromide is used to condensate NaN_3 and nitrile in water (54), (IX) using heterogeneous catalysts, such as Pt NPs, to condense nitrile and sodium azide in dimethylformamide (55).

Table 1: Different methods to synthesize Tetrazoles with five substitutes (55-60).

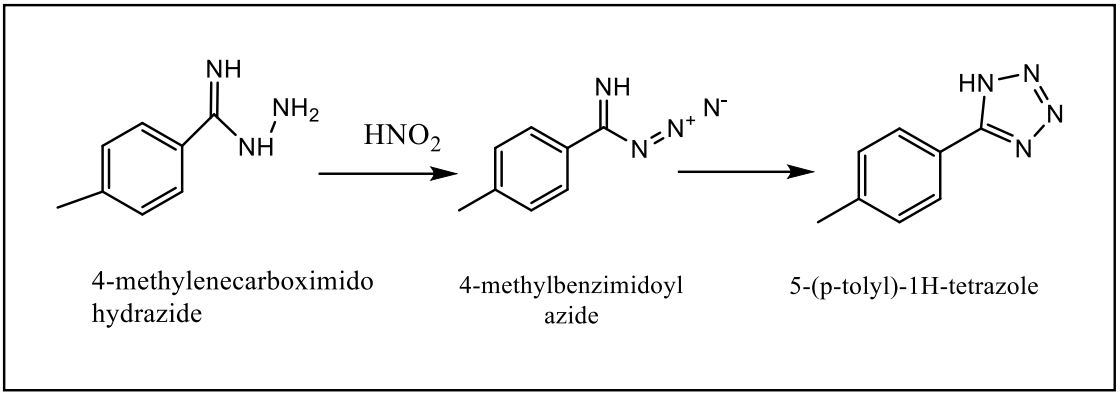
Number	Temperatures, and duration	The solvent and material used	Ref.
I	(--),10-25 min	NaN_3, NH_4Cl, $(C_2H_5)_3$ N.HCl (DMF)	(48)
II	30-100 °C, (--)	NaN_3, $(C_2H_5)_3$N.HCl, toluene	(49)
III	(--), 3-4 days	Nitriles, NaN_3, NH_4Cl, Dodecyl trimethylammonium	(2)
IV	220 °C, 5-30 min	Nitrile, NaN_3, acetic acid, (NMP)	(50)
V	50-120 °C, (--)	TBAF, $TMSN_3$, nitrile	(51)
VI	92-95 °C, (--)	NaN_3, $ZnCl_2$, H_2O	(52)
VII	Reflux	Amide, NaN_3, $SiCl_4$ in MeCN	(53)
VIII	Reflux	$ZnBr_2$, NaN_3, nitrile	(54)
IX	80-130 °C, (--)	NaN_3, nitrile, DMF, cat Pt NPs	(55)



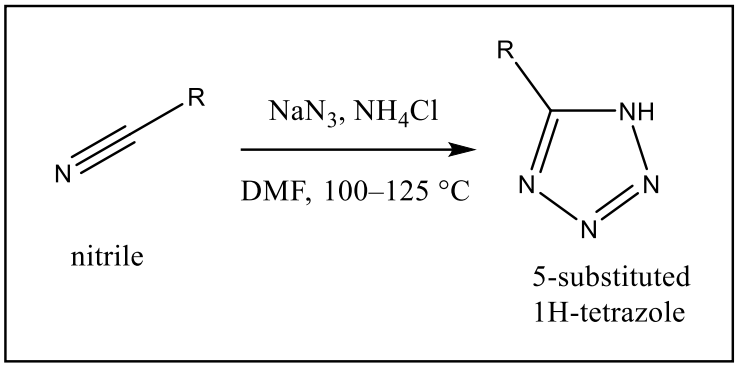
Scheme 2: Different routes to synthesize 5-substituted tetrazoles.

4. SYNTHETIC METHODS OF 1H-TETRAZOLES WITH FIVE SUBSTITUTES

The diazotization of amidrazones was one of the first widely utilized processes for the production of 1H-tetrazoles that are 5-substituted before the [3+2]-cycloaddition process. Hydrazine and imitators were used to create these amidrazones. Using this technique, an imidoyl azide is produced before the 1H-tetrazoles with five substitutes (Scheme 3) (61). Hantzsch and colleagues revealed how to create 5-amino-1H-tetrazole in 1901 by employing azoimide, a hydrazoic acid, and cyanamide (62). Up to the 1950s, the main reactants used to prepare tetrazoles were hydrogen cyanide and hydrazoic acid. Some of these reactants are dangerous; hydrazoic acid, for instance, is extremely volatile, poisonous, and explosive (63). This method also has a number of other problems, including the use of strong Lewis acids and moisture-sensitive reaction conditions (64). This led to further efforts to modify the protocols for the synthesis of 1H-tetrazoles with five substitutes. 1958 saw Finnegan with associates (65), present their fundamental study as well as an improved procedure for producing 1H-tetrazoles with five substitutes from nitriles in DMF by using inorganic NaN_3 and ammonium chloride (Scheme 4).



Scheme 3: 1H-tetrazoles with five substitutes synthesis from amidrazones.



Scheme 4: 1H-tetrazoles with five substitutes are synthesized from nitriles by employing sodium azide and ammonium chloride.

Consequently, safer, faster reaction times and higher product yields have been achieved through the development of novel synthesis techniques. Utilizing microwave (MW) irradiation, reaction times were shortened (43). Over time, research has been done on the use of various catalysts in various reaction settings. The most common catalyst is the Lewis acid (such as $BF_3{\cdot}OEt_2$ (66), $ZnBr_2$ (67), etc.). These catalysts do, however, have drawbacks, such as laborious separation processes and inadequate recovery and recyclable properties. Consequently, to get around these shortcomings, heterogeneous catalysts such as ZnO nanocrystals (68), $CuFe_2O_4$ NPs (69), CoY zeolite (70) Fe_3O_4@SiO_2 (71), Ag NPs (72), $SnCl_2$-nano-SiO_2, Au NPs, graphene, graphene oxide/ZnO nanocomposites, Pt NPs@rGO (57) etc., used to make 5-substituted 1H tetrazoles. Currently, efforts are being made to improve safer and more efficient synthesis techniques.

This section will give a quick rundown of the four methods for making 1H-tetrazoles with five substitutes: microwave-assisted synthesis, heterogeneous catalysts, miscellaneous methods, and NPs as heterogeneous catalysts. However, we will concentrate on using NPs as heterogeneous catalysts in the synthesis of 1H-tetrazoles with five substitutes (Figure 3).

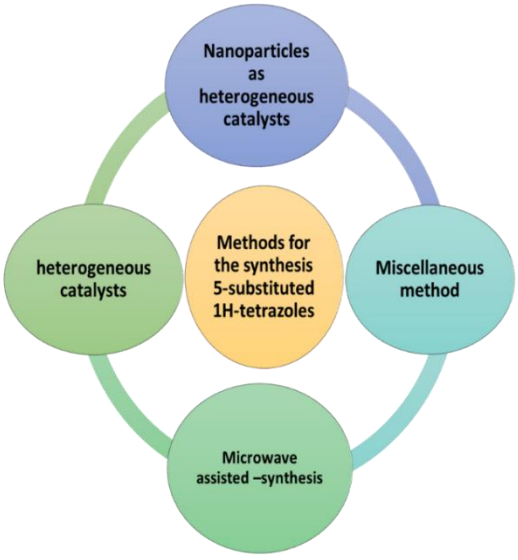
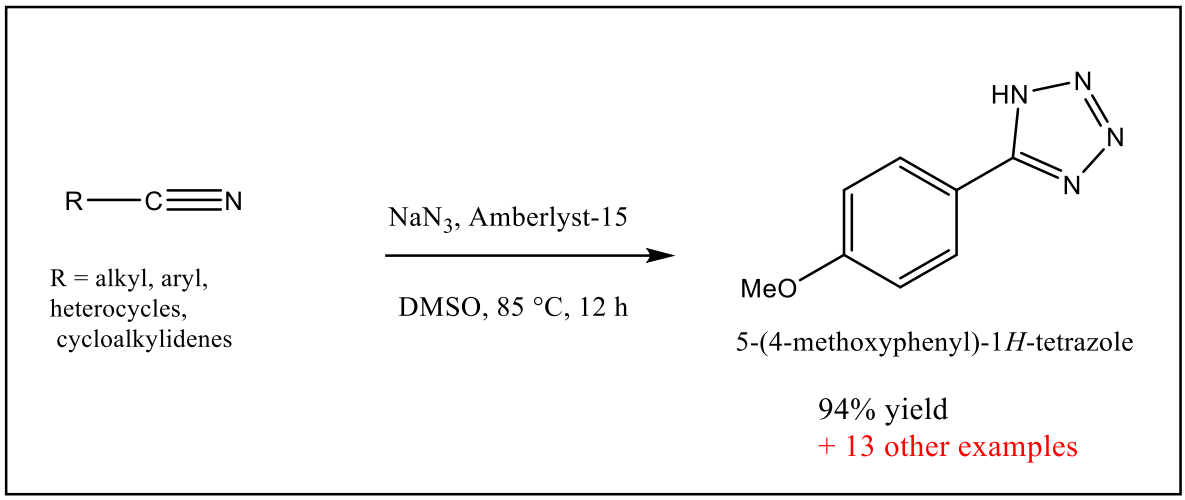


Figure 3: Various methods for producing 1H-tetrazoles with five substitutes Microwave-assisted synthesis.

Another process used to prepare tetrazole derivatives is microwave-assisted synthesis, which we briefly describe as only one method for this preparation. The production of 1H-tetrazoles with five substitutes has difficulties due to extended reaction durations. This disadvantage has been addressed by the use of microwave (MW) irradiation. In 1986, an initial published work involving organic reactions aided by microwaves was released. Despite the expensive expense of specialized microwave equipment, it is nevertheless widely used. It is thought that microwave irradiation produces reactions with higher yields, less time for reaction, and more purity than traditional heating (73-75). Using MW irradiation, Harusawa, and colleagues (76) for the conversion of 1H-tetrazoles with five substitutes in DMF from inert nitriles (Scheme 5).



Scheme 5: Microwave-assisted synthesis of 1H-tetrazoles with five substitutes.

4.1. Heterogeneous Catalysts Synthesis

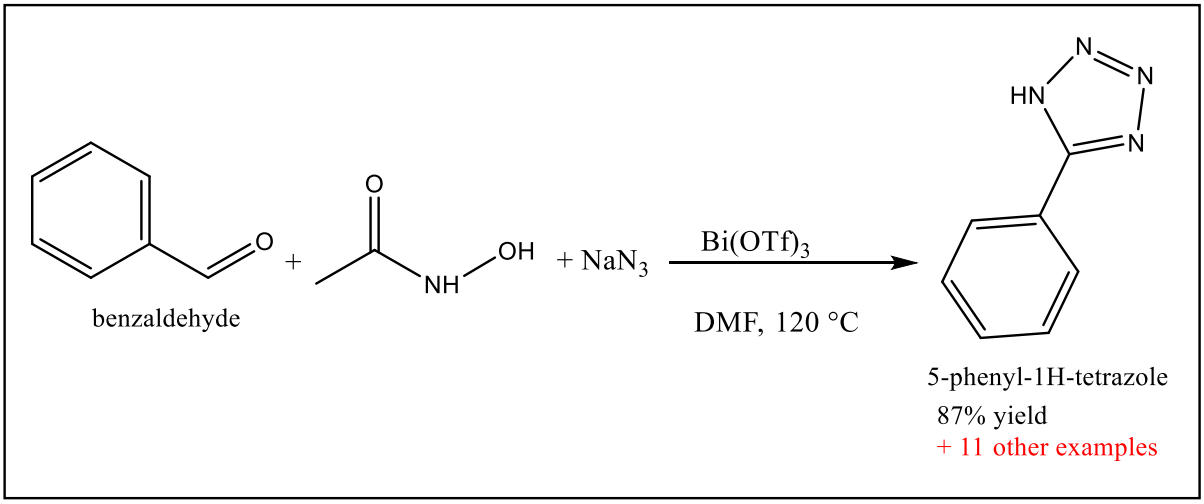
When the phases of the reactants and catalyst are different, this is known as heterogeneous catalysis. Initial homogeneous catalysts for the synthesis of 1H-tetrazoles with five substitutes have low recovery, recyclability, and time-consuming separation processes. Heterogeneous catalysts were created as a solution to these problems, and they are now a common option for the production of 1H-tetrazoles with five substitutes (43). Nagarkar et al. developed a successful process for the synthesis of 1H-tetrazoles with five substitutes using the heterogeneous solid acid resin Amberlyst-15 as a catalyst (77) and employed DMSO as a solvent for 12 hours at 85 °C, yielding a 36-47% product. The highest yield, 94%, was obtained from 5-(4-methoxy phenyl)-1H-tetrazole using 4-methoxybenzonitrile. They employed the catalyst subsequently after recovering it eventually by simple filtration. The Akhlaghinia group employed Cu(II) immobilized on aminated epichlorohydrin-activated silica (CAES) in DMSO as a catalyst for the production of 5-substituted 1H-tetrazoles (59). According to the mechanism, Cu(II) first activates the nitrile's nitrogen atom, accelerating the [3+2] cycloaddition. An acidic workup is then performed to produce 5-substituted 1H-tetrazoles. Up to five reuses of the recovered catalyst were possible. Overall, yields ranged from 75 to 96%, with terephthalonitrile (benzene-1,4-dicarbonitrile) yielding the largest amount of 5-(4-cyanophenyl)-1H-tetrazole (96%).

The preparation of tetrazole derivatives by this method has been tried by many others, each using their methods, and some using the same technique as before, but with some changes in solvent or temperature or so on, some of the heterogeneous catalysts used in these preparations with good and satisfactory yields were $(Ln(OTf)_3$-SiO_2, TBAHS, CAES, and $[bmim]N_3$ ionic liquid (azide source), etc.).

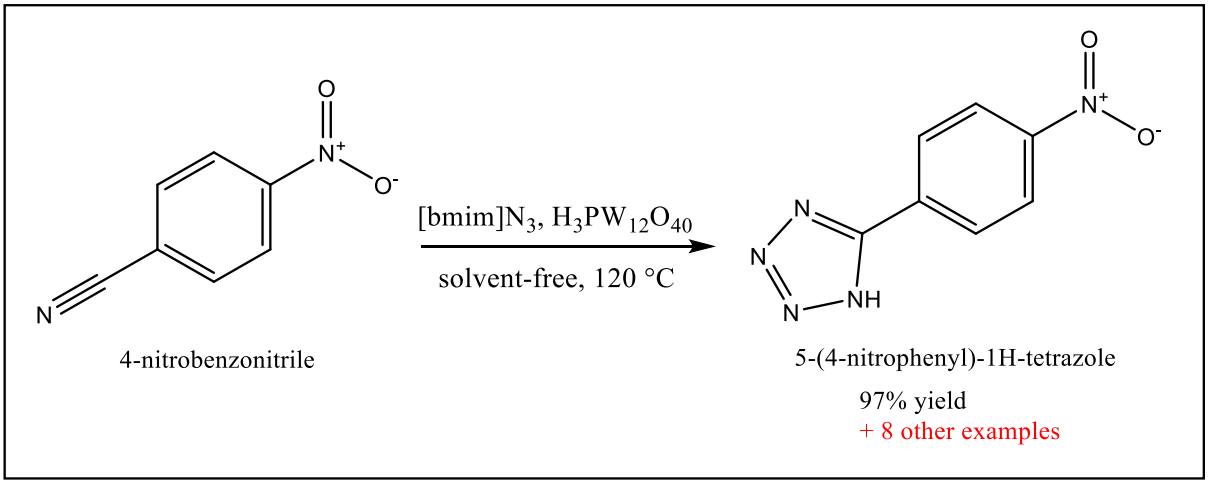
4.2. Miscellaneous Methods Synthesis

This technique is another good technique that gets reliable results including Metal Azide Precursors, Cyclization of Nitriles, Cyclization of Amidines, Cu(I)-Azide-Alkyne Cycloaddition (CuAAC) and additional processes, such as those described by Sridhar and colleagues (78) can synthesize 1H-tetrazoles with five substitutes in a single step, employing bismuth(III) triflate to catalyze the reaction of aldehydes in DMF at 120 °C with sodium azide and acetohydroxamic acid. With moderate to good (60–87%) production, 5-Aryl, 5-Heteroaryl, 5-Alkyl, and 5-Vinyl-1H tetrazoles were synthesized in 15–28 hours. When benzaldehyde was utilized, the highest output was noted (Scheme 6).

Heravi and colleagues reported a solvent-free, green synthesis of 5-alkyl- and 5-aryl-1H-tetrazoles in high yields (89–97%) utilizing nitriles and $[bmim]N_3$ at 120 °C for 5–12 hours. The reaction was catalyzed by heteropolyacid ($H_3PW_{12}O_{40}$) (79). With 4-nitrobenzonitrile, the maximum yield was obtained (Scheme 7).



Scheme 6: $Bi(OTf)_3$-catalyzed synthesis.



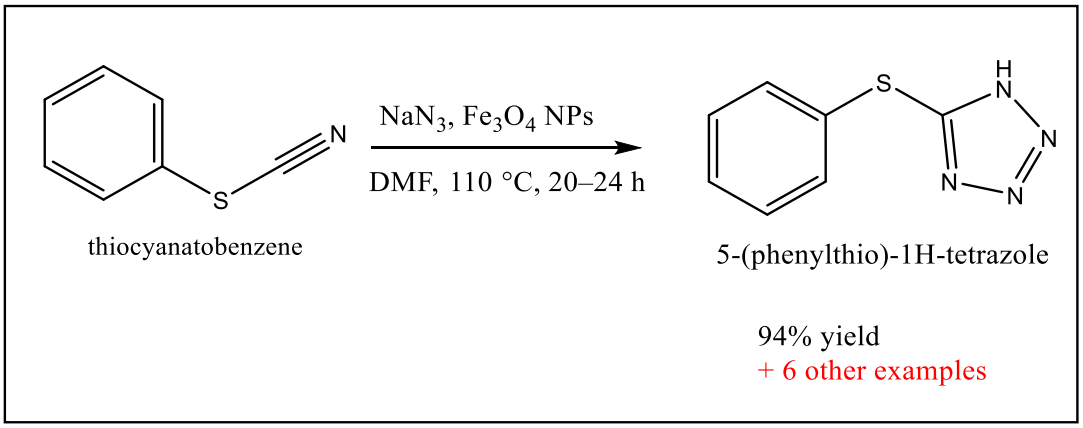
Scheme 7: $H_3PW_{12}O_{40}$-catalyzed synthesis.

4.3. NPs as Heterogeneous Catalysts

In green synthesis, nanomaterials and nanocatalysts are crucial. Benefits like giving the reactant access to a greater surface area and using a minuscule quantity of catalyst to produce meaningful results are attained by shrinking the catalyst. Additionally, it is possible to attain higher selectivity, which will prevent the formation of undesirable products (80) In this section, we will examine some common ways to create the product we want and discuss the importance of each method.

4.3.1. Fe_3O_4 NPs

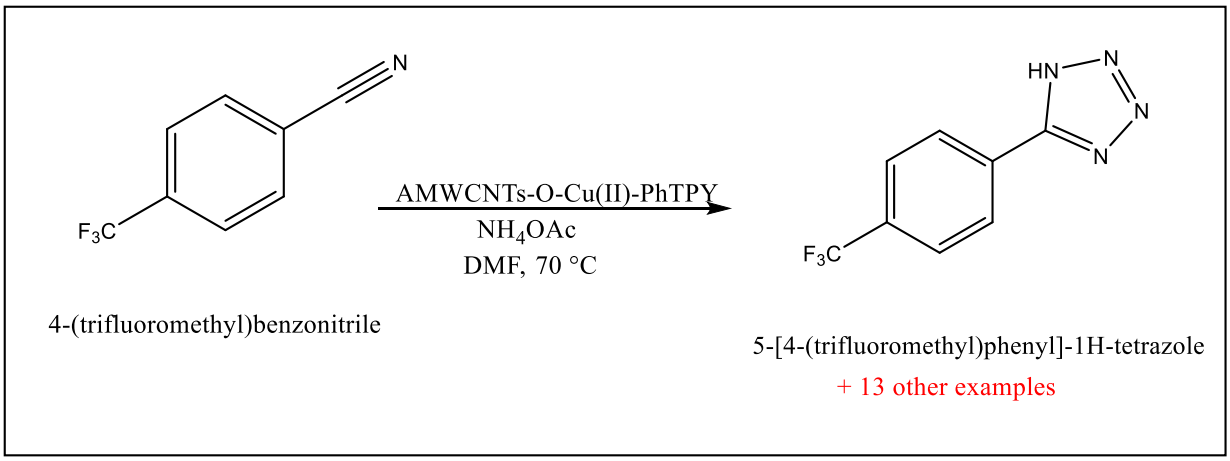
Kolo and Sajad produced 5-(arylthio)-1H and 5-(alkylthio)-1H tetrazoles with yields of up to 94% (81). It employs Fe_3O_4 NPs, which are reused and magnetized recoverable, by using thiocyanates (Scheme 8). The nitrile group of the thiocyanate formed a compound with the catalyst, imparting its electrophilic property, which activated the nitrile group on the catalyst's surface. This is followed by a sodium azide nucleophilic assault. The catalyst's catalytic activity did not significantly decrease throughout its easy recovery and reuse.



Scheme 8: Fe_3O_4 NPs catalyzed synthesis (81).

4.3.2. Cu(II)-O-AMWCNTs-PhTPY NPs

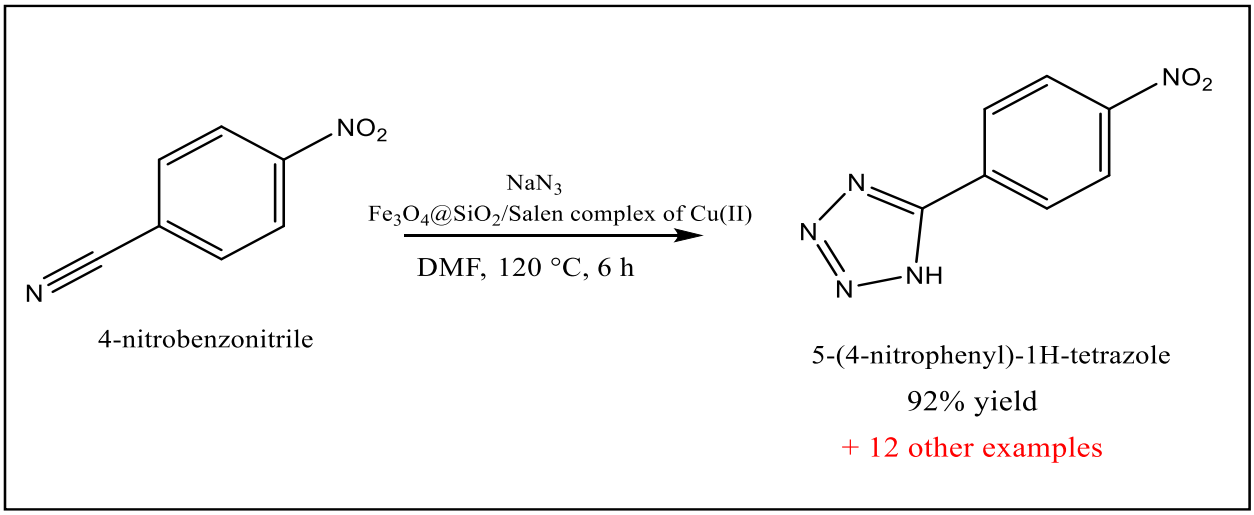
Sharghi et al. produced 1H-tetrazoles with five substitutes with acceptable to good products (75–98%) by immobilizing the 4′-phenyl-2,2′:6′,2″-terpyridine complex onto multiwalled nanotubes of carbon with activation [AMWCNTs-O-Cu(II)-PhTPY] in DMF at a temperature of 70 °C (82) (Scheme 9). Up to five cycles of good reusable were shown by the catalyst (43).



Scheme 9: PhTPY-Cu(II)-O-AMWCNTs catalyzed synthesis (82).

4.3.3. Fe_3O_4@SiO_2/Salen complex of Cu(II) NPs

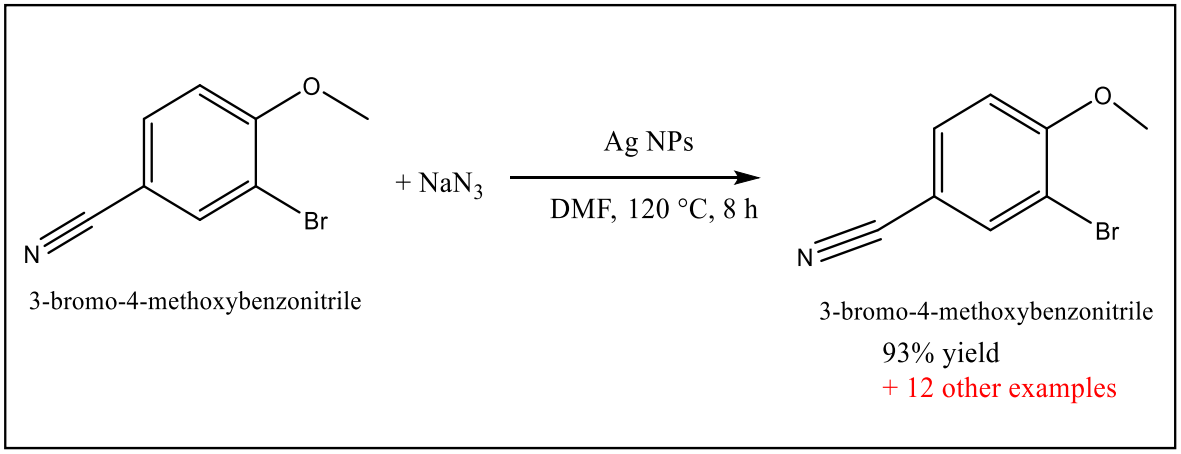
Superparamagnetic Fe_3O_4@SiO_2 NPs [Fe_3O_4@SiO_2 /Salen complex of Cu(II)] are the foundation of the Cu(II) Salen complex. was determined by Sardarian and associates to be the catalyst responsible for the generation of 1H-tetrazoles with five substitutes in DMF at 120 °C (83) seven times without experiencing a discernible decline in activity. It was possible to get a maximum yield of up to 92% by utilizing terephthalonitrile or 4-nitrobenzonitrile (83). In addition to this product, 12 other products can be obtained from this reaction within 6 hours (Scheme 10).



Scheme 10: Cu(II) catalyzed salen compound of Fe_3O_4@SiO_2 synthesis.

4.3.4. Silver NPs (Ag NPs)

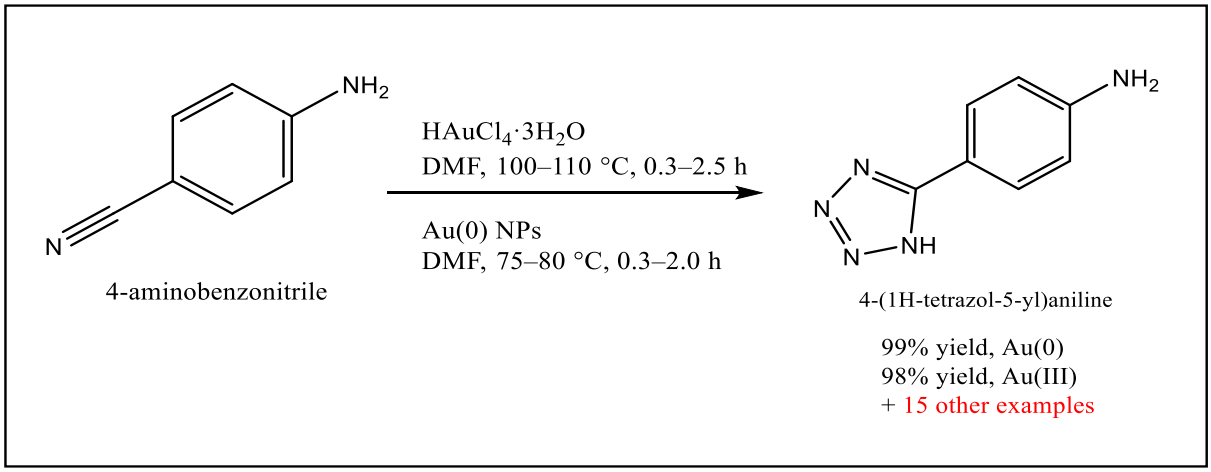
Awasthi and coworkers used silver NPs (Ag NPs) in DMF at 120 °C. (72), for the production of (1H-tetrazoles with five substitutes) that produced 93% yields. Chemically, Ag NPs activate the nitrile group's nitrogen atom, giving the group's carbon atom an electrophilic characteristic. Tetrazoles are also formed as a result of sodium azide's nucleophilic assault. This method does not yield as pleasantly (Scheme 11).



Scheme 11: Using Ag NPs as Catalyzed Synthesis.

4.3.5. Gold (Au) NPs

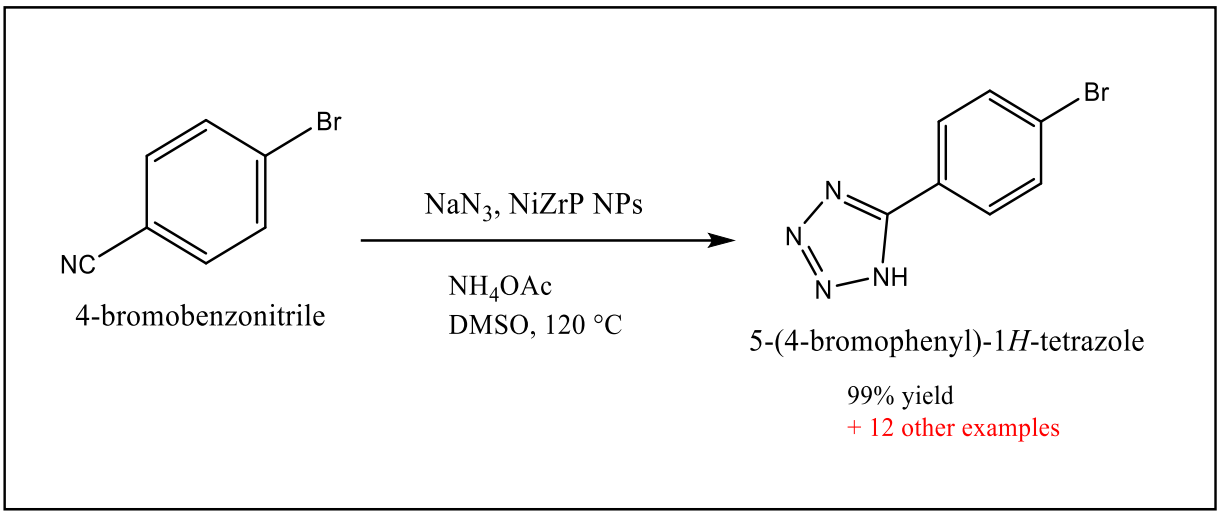
Gold(III) chloride [$HAuCl_4 \cdot 3H_2O$, Au(III)] and gold nanoparticles [Au NPs, Au(0)] were used as catalysts for the synthesis of 1H-tetrazoles with five substituents in DMF, as reported by Awasthi, Agarwal, and colleagues (84). Chemically, the C≡N functionality is first activated by the nucleophilic addition of NaN_3, and it is subsequently activated by protonolysis to produce 1H-tetrazoles with five substitutes through a [3+2]-cycloaddition reaction. For Au(0) NPs, a similar mechanism is expected. Greater reactivity in Au(0) resulted in larger yields in less time. This could be because Au(0) NPs have a higher surface area, which makes it easier for C≡N and Au(0) to coordinate. Five-substituted 1H-tetrazoles were produced in 83–99% yields (16 instances) by using Au(0) NPs, whereas 82–98% yields were obtained by using Au(III) (Scheme 12).



Scheme 12: Au NPs catalyzed synthesis (84).

4.3.6. Nickel zirconium phosphate (NiZrP) NPs

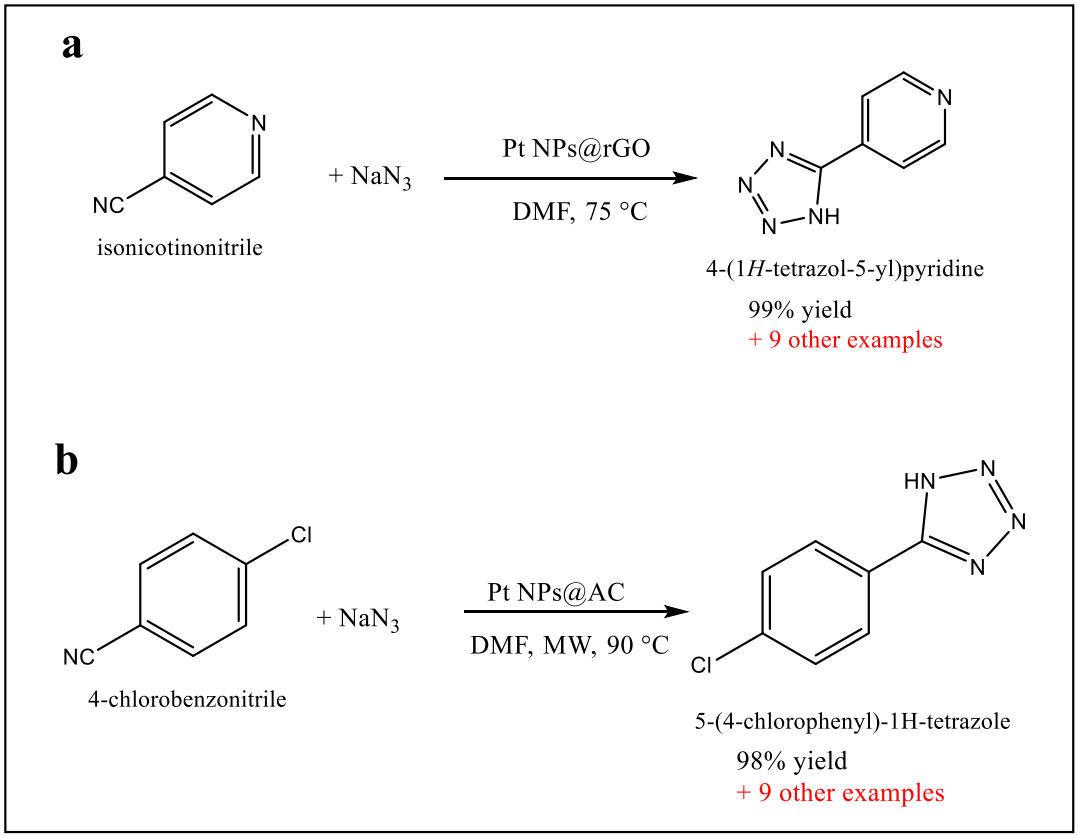
Abrishami and associates used a single nickel zirconium phosphate (NiZrP) nanocatalyst in DMSO at 120 °C to create 1H-tetrazoles with five substitutes (85). Up to five cycles of reuse of the catalyst would not result in a discernible decrease in its capacity to catalyze (Scheme 13). Excellent yields (60–99%) of the 1H-tetrazoles with five substitutes were achieved; the greatest yield was produced by 4-bromobenzonitrile.



Scheme 13: NiZrP NPs catalyzed synthesis (85).

4.3.7. Monodisperse platinum (Pt NPs@rGO) NPs

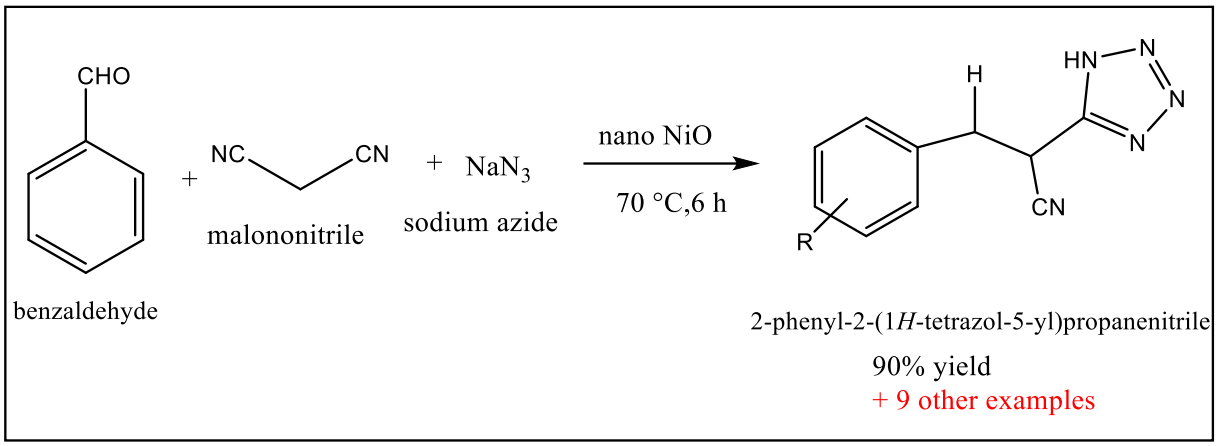
Tetrazole derivatives were produced in a different method by Kaya, Sen, and associates (55). Applying two techniques, the first Using sodium azide, a heterogeneous catalyst known as monodisperse platinum NPs supported by reduced graphene oxide (Pt NPs@rGO) was employed to perform [3+2] cycloaddition on a variety of benzonitriles (55). 5-aryl- and 5-heteroaryl-1H-tetrazoles were generated in good yields (87–99%) in a short reaction time (0.4–5 hours) (Scheme 14a). Up to six times could be retrieved and utilized again without significantly reducing the catalyst's catalytic activity. Second, they prepared another product The subsequent Tetrazoles (5-aryl and 5-heteroaryl-1H) were synthesized with excellent yields (89–99%). Using a brief reaction time (90 °C, 140 W, constant mode, 10–30 minutes) and microwave irradiation in DMF to monodisperse platinum NPs coated on activated carbon (Pt NPs@AC) (Scheme 14.b) (86).



Scheme 14: (a) Synthesis catalyzed by Pt NPs@rGO (55). (b) Pt NPs@AC catalyzed synthesis (86).

4.3.8. Nickel oxide (NiO) NPs

Nickel oxide is one of the latest NP catalysts with unique properties that are widely used in many fields, Safaei-Ghomi J. and Paymard-Samani S. (87) by using a Domino Knoevenagel condensation method to react aldehyde, sodium azide, and malononitrile in DMF for six hours at 70 °C while a nano nickel oxide catalyst was present (Scheme 15).



Scheme 15: Nano-NiO (87).

This table details the conditions, kinds, and quantities of NPs utilized, together with the number of items developed by multiple researchers.

While some have just replicated the work of their forebears with variations in solvent, temperature, NP type, and methodology, others have performed exceptionally well and generated compelling results (Table 2).

Table 2: The conditions and types of NPs used and the amount of products worked on by several researchers.

Entry	Reaction Condition: (T) °C, Time, and reflux	Solvent and yield	Type nanocatalysts	Ref
	110 °C,-,-	DMF, (83-97%)	Fe_3O_4@SiO_2/Schiff base/Cu(II)	(88)
	120 °C, 12 h,-	DMF, (92%)	$CuFe_2O_4$ NPs	(89)
	140 °C,-,-	DMF, (94%)	Cu-MCM-41 NPs	(56)
	-, reflux, 2 h	DMF, (78–95%)	nano-$TiCl_4$·SiO_2	(90)
	110 °C, 15–120 min,-	([bmim]N_3), (70–98%)	Fe_3O_4@chitin	(91)
	120 °C, various,-	(PEG), (60–98%)	Immobilization of Cu(II) on Fe_3O_4@SiO_2@L-arginine	(92)
	-,-, reflux	H_2O/i-PrOH (1:1), (75–94%)	Cu/AC/r-GO nanohybrid	(93)
	130 °C,-,-	PEG-400, (up to 95%)	Cu(II)-Adenine-MCM-41	(94)
	-,-, reflux	H_2O, (96%)	Fe_3O_4@SiO_2-TCT-PVA-Cu(II)	(95)
	120 °C,-,-	PEG-400, (up to 95%)	Pd-SMTU@boehmite	(96)

The following nanocatalysts are employed in the manufacture of tetrazole: (Fe_3O_4 NPs (81), AMWCNTs-O-Cu(II)-PhTPY (82), Fe_3O_4@SiO_2 (83), Ag NPs (72), Au NPs (84), NiZrP (85), Pt NPs@rGO (55), nano-NiO (87), etc). Nitriles and sodium azide undergo [3+2] cycloaddition to complete these syntheses. The utilization of green nanocatalysts in the manufacturing of heterocycles with a specific reaction time, low chemical consumption, high yield, and ease of operation are all advantageous. In most processes, the utilized catalyst may be readily extracted from the reaction mixture and recovered without losing its catalytic activity. Nitriles and sodium azide undergo [3+2] cycloaddition to complete these syntheses. The use of green nanocatalysts in the manufacturing of heterocycles with a specific reaction time, low chemical consumption, high yield, and ease of operation are all advantageous. In most processes, the utilized catalyst may be readily extracted and retrieved without losing its catalytic function from the reaction mixture.

To summarize, the utilization of nanocatalysts in synthesis offers a means of attaining more effective, focused, and environmentally friendly chemical reactions, which has implications for both lab-based studies and commercial uses. Scholars persistently investigate and create novel nanocatalysts to tackle certain synthetic chemistry problems.

5. BIOLOGICAL APPLICATIONS OF TETRAZOLE DERIVATIVES

Tetrazoles are a family of synthetic heterocyclic compounds made up of 2 hydrogen atoms, a single atom of carbon, and 4 nitrogen atoms arranged in a five-member ring (Figure 4). Tetrazole's chemical formula is CN_4H_2. Tetrazole is a crystalline solid that is white to pale yellow in color, soluble in alcohol or water, and has a faint, distinctive smell. It has an acidic nature since it contains four nitrogen atoms (97).

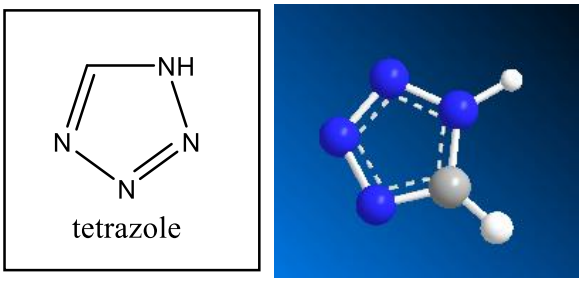


Figure 4: Tetrazole structure.

Numerous uses for tetrazole chemistry are emerging in the domains of biochemistry, medicine, and agriculture (98). The literature has discussed the chemistry of tetrazole derivatives and their medical uses (61). Tetrazole's distinct structure has piqued the curiosity of many in the field of medical chemistry, as have its derivatives. The main reason the tetrazole moiety is important is that it can act as a bioisostere of the carboxylic acid group in supramolecular and pharmaceutical chemistry. Above all, tetrazoles are highly versatile ligands that readily conform to various binding modes.

Derivatives of tetrazole demonstrated antibacterial (99), antifungal (100), anticancer (101), analgesic (102), anti-inflammatory (103), antidiabetic, antihyperlipidemic (104), and antitubercular activities (105). The US FDA has approved a large number of compounds with a tetrazole moiety that are significant for medicine (106). Many studies have been done on the use of tetrazole derivatives in biology, several of which are presented in (Table 3).

Table 3: Some works using Tetrazole derivatives.

Entry	Biological applications	Ref
1.	Antibacterial	(99)
2.	Antifungal	(100)
3.	Anticancer	(101)
4.	Analgesic	(102)
5.	Anti-inflammatory	(103)
6.	Antidiabetic, Antihyperlipidemic	(104)
7.	antitubercular activities	(105)
8.	Anticancer Activity	(120)
9.	Anticonvulsant Activity	(121)

5.1. Anticancer Activity

Numerous research institutions have investigated low-toxicity broad-spectrum medicinal methods (107). They make it rather evident that it can be advantageous if one chemical simultaneously blocks several important pathways and processes (multitherapy). Since patient tumors need to be analyzed for certain mutations to assign patients to the appropriate therapy, many of these treatments can only be loosely referred to as individualized. When considering individual biological variation as a whole, certain mutations only account for the slightest amount of personalization. A far more thorough evaluation of genetic and even lifestyle factors, such as dietary choices, exercise routines, and biobehavioral (stress management) techniques, can be seen in truly customized therapy approaches, along with additional host characteristics including immunological condition and inflammation. The methodical practice of integrative medicine, which was crucial in the creation of this broad-spectrum cancer therapy concept, embodies this kind of personalized treatment (108,109). Two of the actions taken: A variety of steroidal tetrazole derivatives were synthesized by Shamsuzzaman et al. (2014) using a simple technique in two steps. The MTT assay method was used to examine the synthesized compounds' antiproliferative ability in vitro against cervical cancer (HeLa), myeloid leukemia (KCL-22), breast cancer (MDA-MBA-231), and normal cell lines. It was discovered that the class one molecule exhibited significant action (IC50 >60 M) against the three human cancer cell lines while being innocuous to the normal cell lines (110). The MCF-7, MDA-MB-231, and ZR-75 cell lines were employed to test a range of novel substituted tetrazole derivatives that were synthesized by Arshad et al. (2014) (111).

Bhaskar et al. produced a novel class of tetrazole derivatives (2010). With a growth percent of 34–94, compound in (Figure 5) was discovered to be the most effective and potent anticancer drug against ovarian cancer cell lines, SK-OV-3 (112).

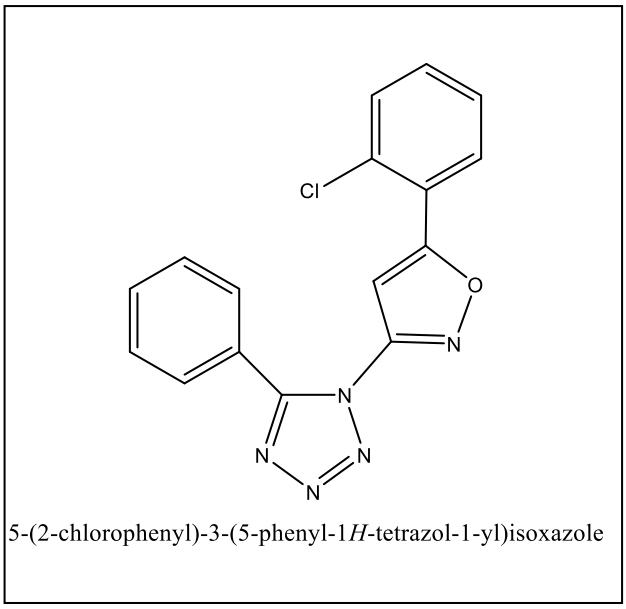


Figure 5: Tetrazole derivative.

5.2. Antimicrobial Activity

Arora et al. (2004) synthesized numerous triazole derivatives using a 5-substituted tetrazole and evaluated their antifungal activity against Candida spp. in vitro, Cryptococcus neoformans, and Aspergillus spp. It has been determined that compound (1) (Figure 6) is a crucial structural element of antifungal efficacy (113). A novel class of substituted-3-mercapto-1, 2, 4-triazoles was synthesized and assessed as an antifungal agent by Collin et al. (2003). Compound (2) (Figure 6) shows significant efficacy in inhibiting *Candida tropicalis* and *Candida albicans* (114). Many others have worked, but we have mentioned only these two.

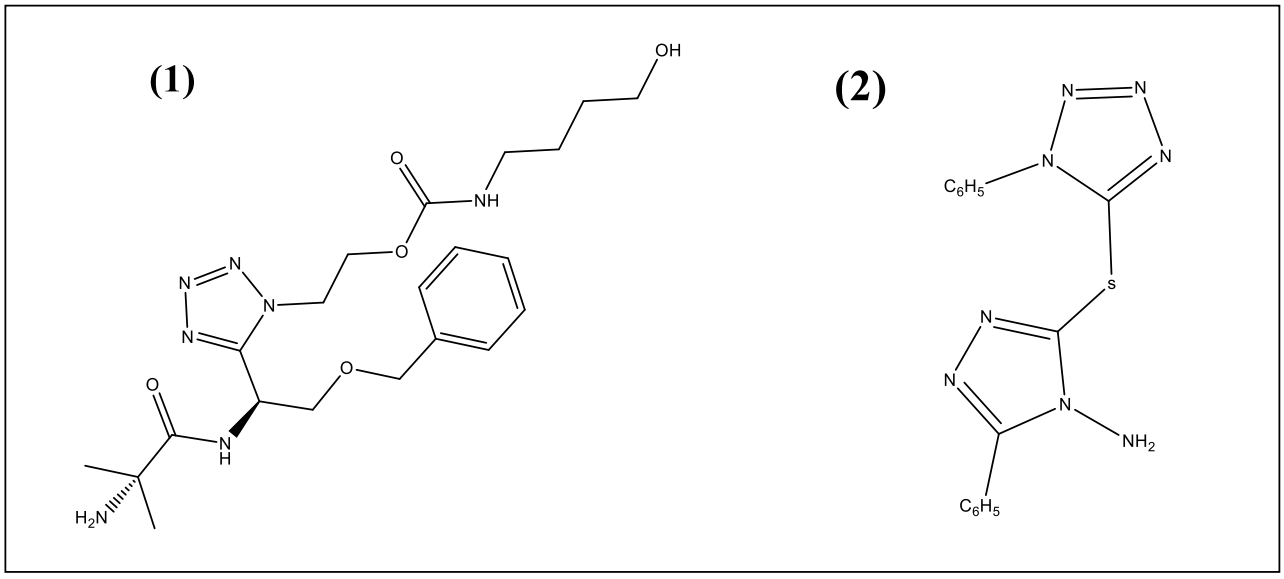


Figure 6: Compounds (1) and (2).

5.3. Antioxidant Activity

Elmegeed et al. (2011) produced a novel family of derivatives of indolyl tetrazolopropanoic acid. (Figure 7.a) had been discovered to possess antioxidant qualities that could be effective against oxidative stress brought on by ACR treatment (115).

A unique series of 3-substituted-5-(1-phenyl-1H-tetrazole-5-yl) methyl)benzene-1,2-diol was synthesized by Adibi et al. (2011). Using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and reducing power test method, the antioxidant activity was carried out. Of the molecules that were produced, (Figure 7.b) demonstrated a higher level of antioxidant activity (116).

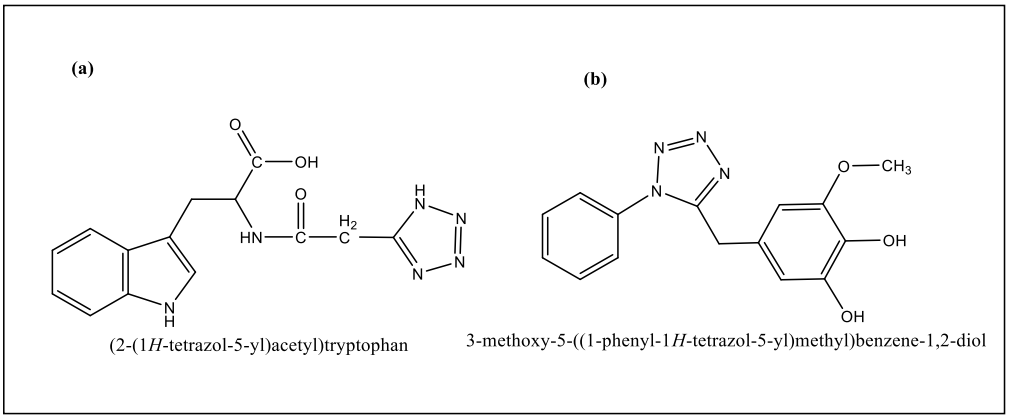


Figure 7: (a) 2-(1H-tetrazol-5-yl)acetyl)tryptophan, (b) 3-methoxy-5-((1-phenyl-1H-tetrazol-5-yl)methyl)benzene-1,2-diol.

5.4. Anti-diabetic Activity

Gao et al. (2010) synthesized tetrazole (117) using N-glycosides as SGLT2 inhibitors and tested the drug's hypoglycemic effects in vivo on mice using the oral glucose tolerance test (OGTT). The most potent molecule against the common drug dapagliflozin was found to be one particular one. Nicolaou and colleagues employed pyrrolyl-tetrazole derivative as a nonclassical bioisostere of a carboxylic acid moiety. (2010) created a novel series of compounds and assessed their ability to inhibit aldose reductase in vitro. The observations suggest that a compound exhibited strong antioxidant action, and the isomers of pyrrolyl-tetrazole were putative starting points for the synthesis of drugs of selective aldose reductase. See the (Figure 8).

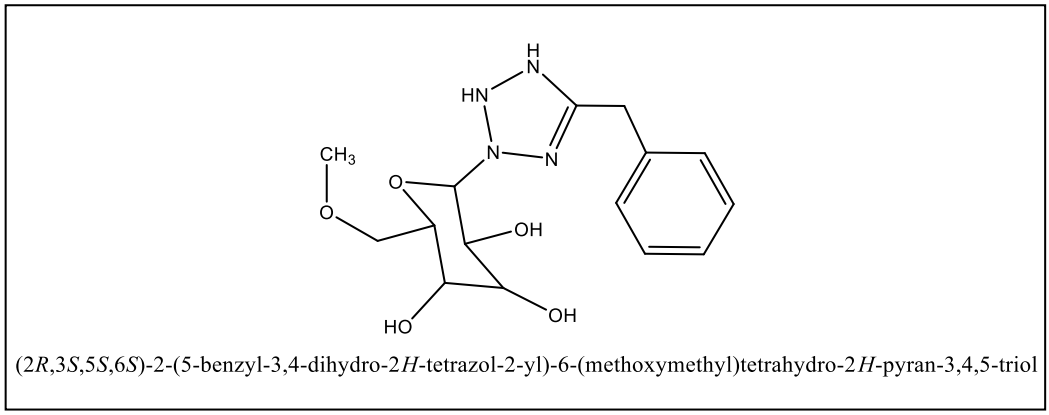


Figure 8: Tetrazole derivative.

5.5. Anti-HIV Activity

Uraglian et al. (2006) developed a novel family of aryltetrazolylacetanilides and assessed them as HIV-1 non-nucleoside reverse transcriptase inhibitors using the therapeutically relevant K103N mutant strain (118). 5-(phosphonomethyl)-1H-tetrazole was created by Hutchinson et al. (1985), who then assessed its effectiveness against the Herpes Simplex Viruses-1 replication, DNA polymerase inhibitor action, and virus of influenza type A RNA transcriptase activity (119). See the compounds in (Figure 9).

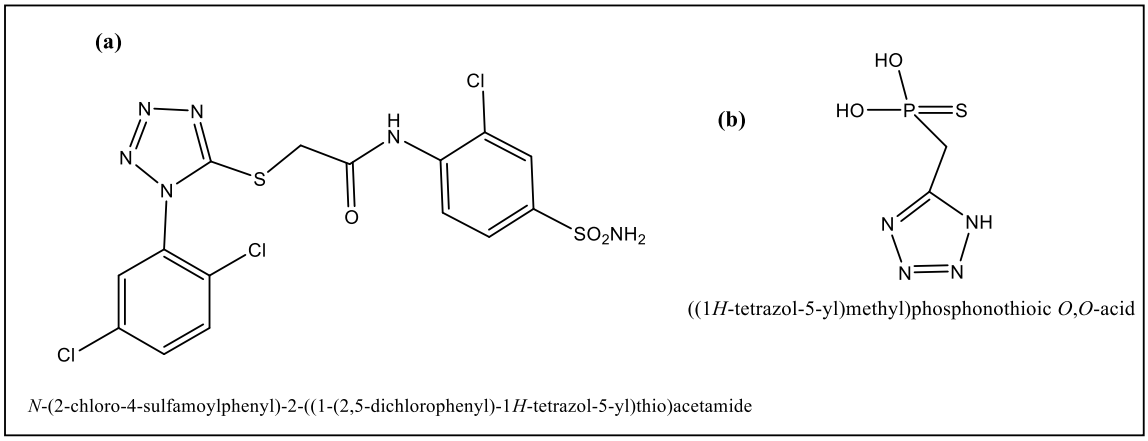


Figure 9: Anti-HIV tetrazole derivatives compounds.

6. CONCLUSION

Tetrazoles are important heterocyclic analogs found in many different chemical and pharmaceutical substances. Following the synthesis and analysis of each of these studies on the tetrazole derivative preparation. Although there are many ways to synthesize these tetrazoles, a green synthetic method is quite effective. Particles with a distinct view of the boundary of something at the nanoscale are known as NPs, and they are less than 100 nm by at least one magnitude. Using nanocatalysts is one of the most popular green synthesis methods for producing tetrazole derivatives. Nitrides and sodium azide undergo [3+2] cycloaddition to complete these syntheses. The utilization of green nanocatalysts in the manufacturing of heterocycles with a specific reaction type, high yield, quick reaction time, little chemical consumption, and ease of operation are all benefits. In the majority of operations, the utilized catalyst may be readily removed and repurposed without losing its catalytic activity from the reaction mixture.

Tetrazole and its derivatives, belonging to the nitrogen-containing heterocycle family, have a wide range of biological actions, including antibacterial, antifungal, anticancer, analgesic, anti-inflammatory, antidiabetic, anti-hyperlipidemic, and antitubercular effects. This review discusses the biological relevance, uses, and distinctive qualities of tetrazole. The many synthesis methods and varied biological activities of substituted tetrazole derivatives are reviewed in this inquiry. This study aimed to gather the literature work offered by researchers on tetrazole for their diverse biological actions, in addition to reporting on current efforts done in this area.

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