Journal of Science and Technology
ISSN: 2456-5660 Volume 9, Issue 08 (August -2024)
www.jst.org.in *DOI:https://doi.org/10.46243/jst.2024.v9.i08.pp01- 34*

RESEARCH PROGRESS ON TETRAZOLE DERIVATIVES

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To Cite this Article
Abubakar Muhd Shafi'i, Sabiu Rabilu Abdullahi, Ritu Sharma, Abubakar Dahiru, Mustapha Sulaiman**,** **"RESEARCH PROGRESS ON TETRAZOLE DERIVATIVES** *Journal of Science and Technology, Vol. 09, Issue 08,- August 2024, pp01-34*

Article Info

Received: 07-04-2024 *Revised: 09-05-2024* *Accepted: 20-07-2024* *Published: 06-08-2024*

ABSTRACT

This review explores the latest developments in the synthesis of tetrazole derivatives, including mono-, 1,5H-, and 2,5H-substituted forms. Scientific study has recorded the diverse biological and clinical applications of these chemicals, which have attracted attention due to their demonstrated roles in antiviral, anti-tuberculosis, anticancer, antimalarial, and anti-inflammatory actions. While the distinctive structural features of 1,5H-disubstituted and 2,5H-disubstituted tetrazoles contribute to their distinct pharmacological profiles, the flexibility of mono-substituted tetrazoles highlights their potential across a range of therapeutic applications. The process of synthesizing these derivatives is essential to increasing their usefulness in drug development and presents encouraging opportunities for the creation of novel therapeutic agents. The important developments in tetrazole chemistry are highlighted in this study, along with their possible influence on the advancement of pharmaceutical innovation and biomedical research in the face of various medical issues.

Keywords: Tetrazole, Heterocyclic, Anticancer, Antituberclosis.

1. INTRODUCTION

Scientists and chemists have been enthralled by heterocyclic compounds for ages due to their distinctive ring structures that include at least one heteroatom, because of the various nature of these molecules. The term "heterocycle" comes from the Greek words "heteros," which means different, and "kyklos," which means ring. Contrary to their carbocyclic counterparts, heterocyclic compounds possess special qualities due to the inclusion of heteroatoms such nitrogen, oxygen, sulfur, and occasionally additional elements [1]. These compounds belong to a broad class of organic molecules and are essential to the study of biology, chemistry, and materials science. These substances have a cyclic ring structure with at least one heteroatom, an atom other than carbon. These compounds have special qualities due to the presence of heteroatoms like nitrogen, oxygen, sulfur, or other elements. For this reason, heteroatoms are crucial in the synthesis and design of medications, agrochemicals, functional materials, and other substances [2]. Tetrazole is classified as a heterocyclic chemical, meaning that it is a five-membered ring that has four nitrogen atoms and one carbon atom [3]. It is a six-electron aza molecule with five members, and the reactivity of 5-substituted tetrazole is comparable to that of aromatic compounds. Tetrazole is defined as a heterocyclic compound, a five-membered ring that contains carbon with four nitrogen atoms [3]. The parent tetrazole is found in three isomers, 1H-, 2H-, and 5H-tetrazole [4]. It is a five-membered aza compound with 6π electrons. 5-substituted tetrazole reactivity is comparable to aromatic compounds. The Huckel 6π electrons are satisfied by four ring electrons and one loan pair of nitrogen electrons. The acidic nature of tetrazole is comparable to corresponding carboxylic acids, but ring tautomerism of tetrazoles differs from carboxylic acids. Tetrazole's acidic nature is mostly influenced by the type of the replacement compound at the C-5 position. Resonance stabilization causes the 5-phenyltetrazole anion to exhibit a strong acidic character similar to benzoate. Tetrazole reacts with metal hydroxides to form the tetrazole anion, which may be produced easily and is stable at high temperatures in both alcoholic and aqueous solutions [5, 6]. Tetrazole has a melting point between 155 – 157 ^{o}C. It break down and release harmful nitrogen fumes when heated. When exposed to stress, fire, and heat from friction, these rupture violently [5].

In 2022, Dalal made the discovery of the tetrazole compound [7]. The research conducted in the area by American and European scientists is widely known among scientists. Some of the

renowned scientists R. Henry, R. Huisgen, R. Butler, E. Lippmann, M. Begtrup, B. Stanovnik, J. Plenkievich, J. Elguero, M. Palmer, and A. Katritzky are among those the researchers would want to select. Tetrazole chemistry has seen significant advancements thanks to Russian scientists [8].

Tetrazoles can be made by a number of methods, the most common of which is the "traditional method," which involves the [3+2] cycloaddition of azides and organic nitriles. This approach has been utilized for many years in the synthesis of tetrazoles [9]. The Modern and Green Synthesis Methods are two additional techniques for synthesizing tetrazole chemicals and derivatives. The former group comprises those that use ultrasound or microwave irradiation to speed up the cycloaddition reaction [9], while the latter group seeks to reduce environmental impact and enhance sustainability [10]. One area that traditionally supports the advancement of tetrazole chemistry is the creation of novel medications. The number of studies examining the biological activities of substances containing the tetrazole ring has sharply increased over the last several decades [11]. Tetrazole exhibits a wide range of biological properties, including anti-bacterial [12], anti-cancer [13], anti-fungal [14], anti-inflammatory [15], anti-malarial [16], anti-tubercular [17], and anti-viral [18, 19] activities, through its non-covalent interactions with different enzymes and receptors in organisms. Additionally, there are other pharmaceutically significant compounds with tetrazole moiety that have been licensed by the US Food and medication Administration for the treatment of various disorders. Examples of these compounds include the antibacterial agent Ceforanide and the anti-asthmatic medication Tomelukast. Tetrazole derivatives are therefore interesting for the creation of novel medications [20].

The scientific literature contains numerous synthesis procedures for tetrazoles derivatives. Tetrazole derivatives can be synthesized in a number of ways, such as with triethyl orthoformate, sodium azide, alcohols, aldehydes, and isocynides. These substances have a wide range of biological applications, including anti-inflammatory, anti-fungal, anti-cancer, and anti-malarial activities. They are used in anticancer, antimycobacterial, antidiabetic, and anticonvulsant medications because of their planar shape, which promotes receptor connections. Gaining knowledge of tetrazole derivatives paves the way for innovations based on their distinct scaffolds in the future.

2. SYNTHESIS OF TETRAZOLE DERIVATIVES

Tetrazoles are often classified into three groups based on the substituent number: parent, monosubstituted (**A)**, and disubstituted tetrazoles (**B)** [21] (fig.1).

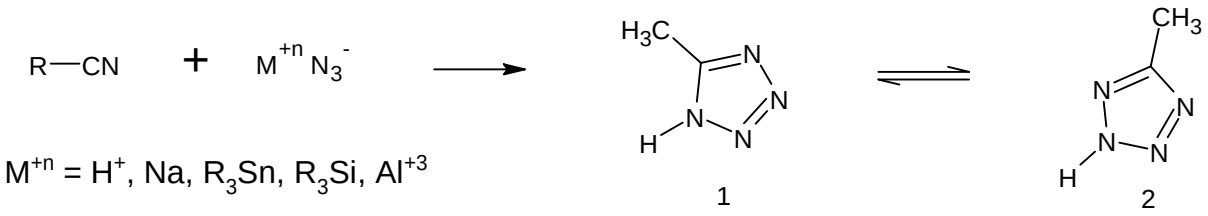
Figure 1. *Structures of Tetrazole*.

Tetrazoles are made by a number of methods, most of which involve the use of azides as reaction intermediates or starting materials [22]. New methods of producing this heterocycle are being worked on utilizing a variety of techniques, including electrochemical methods [23], which use the reaction of azides with hydrazones to form tetrazoles. The subsequent sections address the latest advancements in the synthesis of tetrazole derivatives, with the main objective being to present and deliberate on techniques that can be employed in the creation of innovative active molecules possessing biological activity.

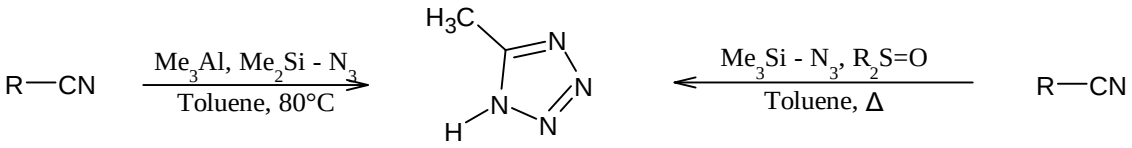
2.1 5-Substituted 1H-Tetrazoles

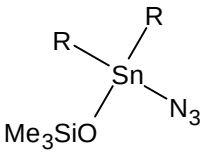
The optimum synthetic approach for making tetrazole is often determined by its composition and substitution pattern. Recent literature studies have, for the most part, been either refinements or extensions of current methodology. Reacting nitriles with azide ion yields 5-substituted-1H-tetrazoles in the most convenient way (Scheme 1). In most situations, good yields of tetrazole products are produced by heating a mixture of nitrile, sodium azide, and a proton source (to generate hydrazoic acid in situ) in a suitable solvent (e.g., dimethylformamide) at a moderately high temperature [24]. To prepare 5-(phosphonomethyl)-1H-tetrazole **3** [26] and the 1H tetrazol-5-yl analogues of arachidonic **4** and linoleic acids **5** in moderate yields, aluminum triazide [25], was synthesized in situ from aluminum trichloride and sodium azide [27]. This reagent's disadvantage is that it produces two moles of hydrazoic acid for every mole of product during hydrolytic work-up. Tetrazoles **1** were produced by treating aliphatic or aromatic nitriles with

"ecpimolar" trimethylaluminum and trimethylsilylazide, as Digambar and Varala showed [28]. To obtain good to exceptional yields of tetrazoles, 1.5 mole equivalent of each reagent was typically utilized (Scheme 2). High levels of hindrance in nitriles (R = r-Bu, Ph, MeC-) led to low yields and reduced conversion. In this reaction, trimethylaluminum most likely functions as a Lewis acid, activating the nitrile in the direction of azide addition. The reaction must be quenched carefully though, as it may be exothermic and exhibit rapid gas evolution. A reagent commonly prepared in situ from sodium azide and volatile and poisonous trialkyltin chloride can be used as an alternative to trialkyltin azide [29]. According to Mazlouni and Shirni, 5-substituted-1H-tetrazoles **1** (Scheme 2) is produced by the effective reaction of trimethylsilyl azide with nitriles in the presence of dialkyltin oxide [30].It was proposed that dialkyl (0-trimethylsilyl)-azidostannylhydrin 6 was the reactive intermediate. Alexis et al. [31] reported a high yielding production of the di(alkali metal) salt of 1H-tetrazole-5-carboxylic acid **7** by reaction of an alkali tnetal azide with an alkyl cyanoformate (Scheme 3) It has been demonstrated that these substances are helpful intermediates in the synthesis of 1H-tetrazole-5-carboxanilides **8**, which have therapeutic potential for allergic disorders. The corresponding dicyanvacetates **9** and trimethylsilyl azide were synthesized in chloroform at room temperature to get Z-(1H-Tetrazol-5-yl)-2-cyanoacetate betaines **10** [32].



Scheme 1. *Synthesis of 5-substituted-1H-tetrazoles by reacting nitriles with azide ion.*





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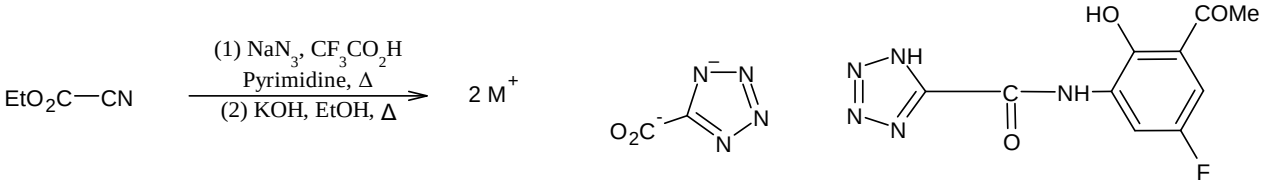
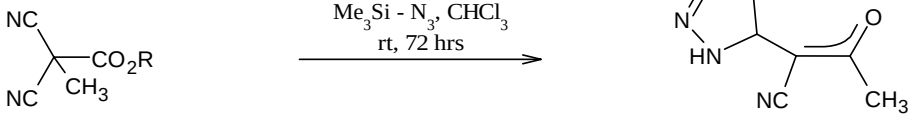
Scheme 2. *Synthesis of 5-substituted-1H-tetrazoles by the effective reaction of trimethylsilyl azide with nitriles in the presence of dialkyltin oxide*.



7 8



9 10

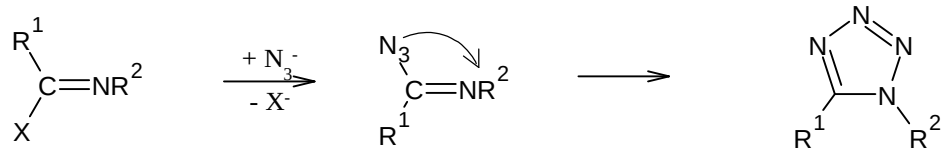
Scheme 3. *Synthesis of 1H-tetrazoles carboxylic acid.*

2.2 1,5-Disubstituted Tetrazoles

The majority of the several pathways that lead to 1,5-disubstituted tetrazoles **13** end with the 1,5-electrocyclization of an imino azide **12** (-C(N,)=N-) specie[33]. The displacement of an imidoyl halide **11** by an azide ion is a commonly employed and practical method for creating imino azide

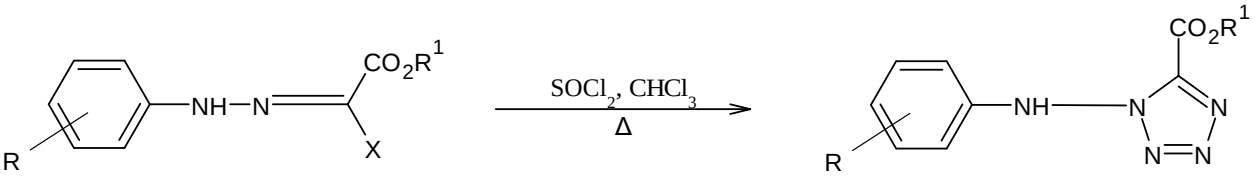
intermediates (Scheme 4) [34]. When amides react with phosphorus pentachloride or thionyl chloride, imidoyl chlorides are easily produced. An analogous case was recently described by Preetham et al, in which phase-transfer conditions (Scheme 5) were used to convert hydrazonyl chlorides **14** to the equivalent azidohydrazones **15** using sodium azide [35]. Unexpectedly, compound **15** showed little interest in cyclizing to produce 1-aryIamino-5-carboalkoxytetrazoles **16**. To polarize the system, different Lewis acids were added, which caused the electrocyclic closure. Using two molar equivalents of thionyl chloride produced the greatest results.

Comparable methods with heteroatoms as the leaving group instead of halides have been published. Bojarska et al. reported the reaction between trimethylsilyl azide and an oxyphosphonium salt 18 (made from the corresponding amide **17** under Mitsunobu conditions), which produced the 1,5-disubstituted tetrazole **13** [36]. The 1-(N-(2-cyanoethyl))-5-substituted tetrazole products **13**, (R2 = CH,CH,CN) could be easily N-dealkylated by aqueous base treatment to generate the 5-monosubstituted tetrazoles **1** in the case of an N-(2-cyanoethyl)-substituted amides. This approach ought to be particularly helpful in situations where an N-protected tetrazole is needed. It was shown that chirality may be preserved during the synthesis of phenylalanine, an a-amino acid using a tetrazole counterpart. 1,5-disubstituted tetrazoles (Scheme 6) were produced by treating irnidoyltriflates **19**, which were produced in situ from amides and trifluorornethanesulfonic anhydride, with sodium azide [37]. There have also been instances of displacements for sulfur [40], oxygen [39], and nitrogen [38] (Scheme 7). Basu and Ghosh have reported addition-elimination reactions of nitrogen nucleophiles to 3,3-diazido-2-cyanoacrylats **20** in a number of papers. Primarily, these reactions result in vinyl azides **21**, which then undergo basic 1,5-electrocyclization to produce dihydrotetrazolylidene cyanoacelates **22** in a good to excellent yield (Scheme 8) [41]. Additionally, substituted hydrazines (and amidrazones) can be made by hydrazinolysis of Bimidoyl derivatives carrying leaving groups **24** to yield imidoyl azides by diazotization.



11 12 13

Scheme 4. *Synthesis of 1,5-Disubstituted Tetrazoles.*



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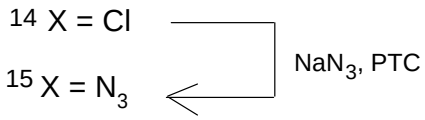
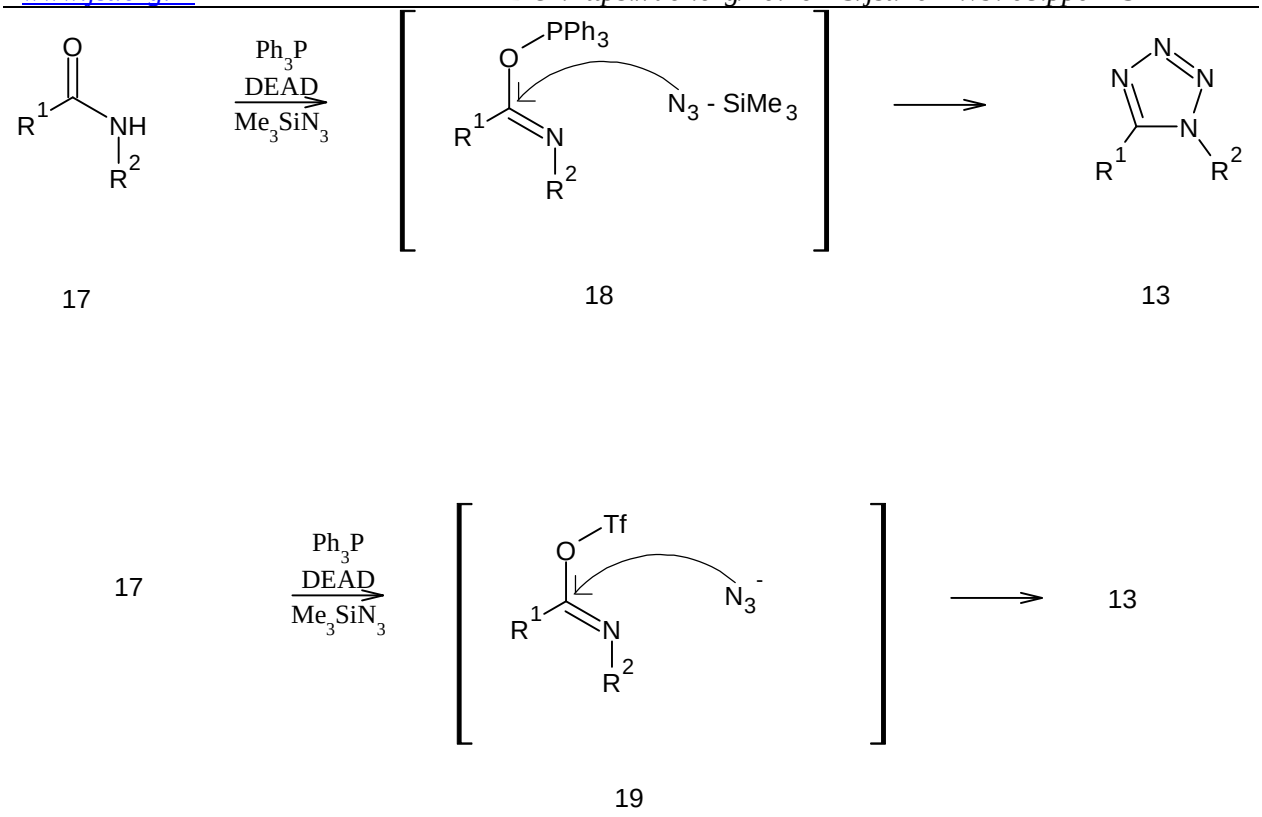
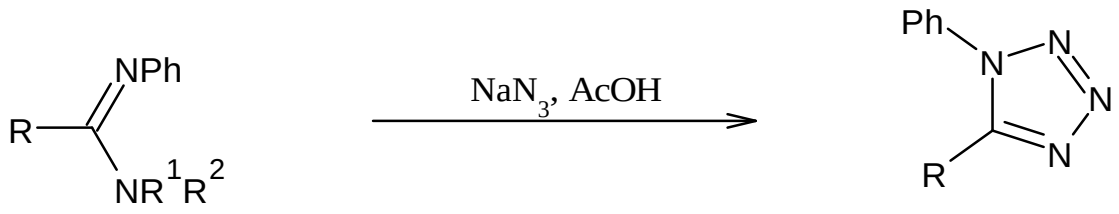
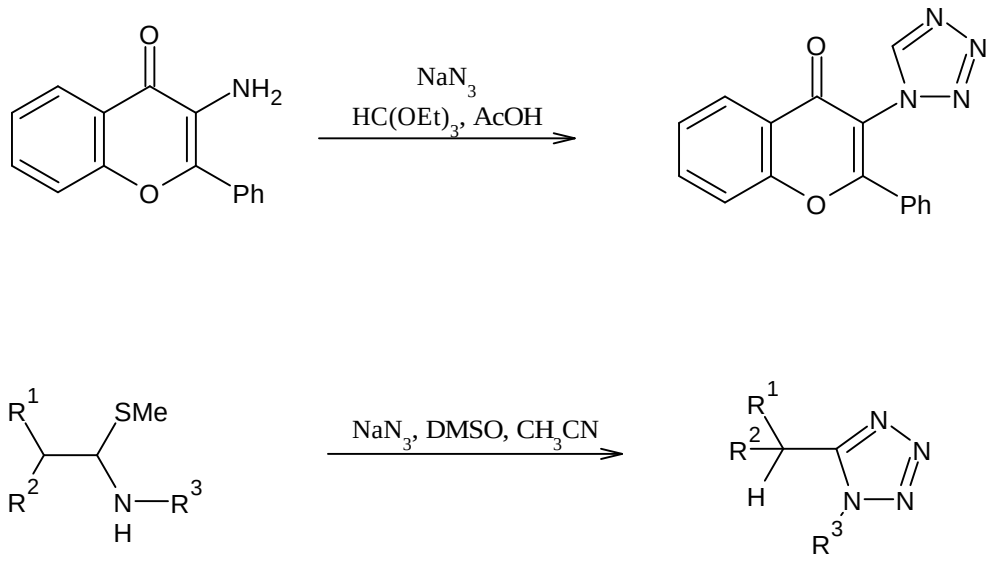


Scheme 5. *Phase-transfer conditions for the convertion of hydrazonyl chlorides to the equivalent azidohydrazones using sodium azide.*

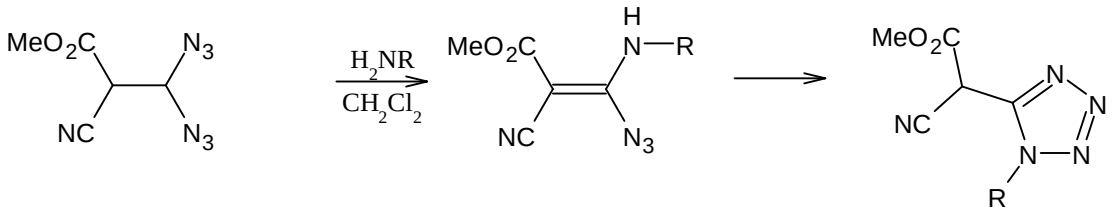


Scheme 6. *Synthesis of 1,5-Disubstituted Tetrazoles.*



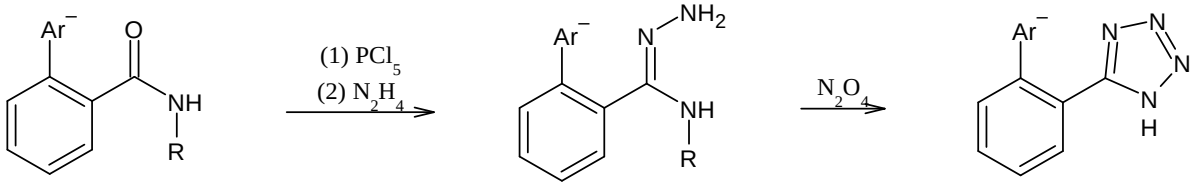


Scheme 7. *Examples of Nitrogen, oxygen and sulphure displacement reaction.*



20 21 22

Scheme 8. *Synthesis of dihydrotetrazolylidene cyanoacelates.*



Ar = 4 - MeC_6H_4, R = CH_2CH_2CN 23 24

Scheme 9. *Synthesis of substituted hydrazines.*

2.3 Synthesis of 2,5-disubstituted tetrazole derivatives

Megha G. et al. (2023) used a multi-step procedure to synthesize new 2, 5-disubstituted tetrazole derivatives (7a-g). First, using potassium carbonate as a catalyst, n-(triphenylmethyl)-5-(4'-bromomethylbiphenyl-2-yl-) terazole and ethyl-piperidine-4-carboxylate reacted in DMF. The reaction eliminated hydrogen bromide and produced the yield 2-(N-triphenylmethyl tetrazolyl)-methyl biphenyl ethyl piperidine-4-carboxylate. The final 1-((2'-(2-(2-(substituted phenyl)) was obtained by reacting potassium carbonate with substituted phenacyl bromides in solvent media after triphenyl was removed using a mixture of 4N HCl in methanol (20 mL) solvent to obtain methyl biphenyl tetrazolyl-ethyl piperidine-4-carboxylate. Hydrolyzing the compound led to a stable compound. 2-Oxoethyl-2H-tetrazol-5-yl[1,1'-biphenyl]Solid compound derived from 4-yl)methyl)piperidine-4-carboxylic acid [43]. Their IR, 1 H-NMR, 13 C-NMR, and mass spectra verified the structures of the novel 2, 5-disubstituted tetrazole derivatives.

3. PHARMACOLOGICAL ACTIVITY OF TETRAZOLE DERIVATIVES

Tetrazole is used in many different applications, such as explosives, propellants, and catalysts. Despite this, their wide range of biological activities (fig. 2) and distinct electrical characteristics helped them to establish a reputation in the field of medicinal chemistry [44]. Many tetrazole derivatives have been tested in recent years for their potential as anti-inflammatory, analgesic, anti-cancer, anti-convulsant, anti-hypertensive, hypoglycemic, anti-parasitic, anti-viral, anti-tubercular, and anti-malarial agents. A number of these compounds showed encouraging in vitro and in vivo potency. The biological activities of tetrazole derivatives both in vitro and in vivo are reviewed, along with their recent advancements.

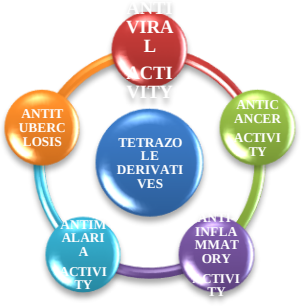


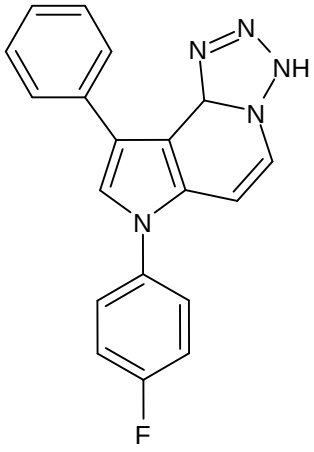
Figure 2. *Biological acitivities of Tetrazole Derivatives.*

3.1 Anti-tubercular activity

The primary cause of tuberculosis (TB) is Mycobacterium tuberculosis (MTB), which is widely distributed throughout the world [45,46]. Globally, an estimated 1.7 billion people have contracted MTB, and 5–10% of people will get TB illness at some point in their lives. As the most common infectious agent-related cause of death, tuberculosis (TB) claimed the lives of an estimated 1.6 million individuals worldwide in 2017 [47]. It is crucial to develop new anti-TB drugs since drug-resistant TB (DR-TB) and TB co-infected with HIV pose significant obstacles and jeopardize efforts to manage this epidemic [48]. Lipophilicity is a crucial factor in the membrane penetration of substances into MTB cells, and merely making a medication more lipophilic can enhance its anti-TB properties [49]. Tetrazole derivatives have the potential to be anti-TB medicines because tetrazole has the ability to improve lipophilicity, which helps chemicals pass through the plasma membrane [50].

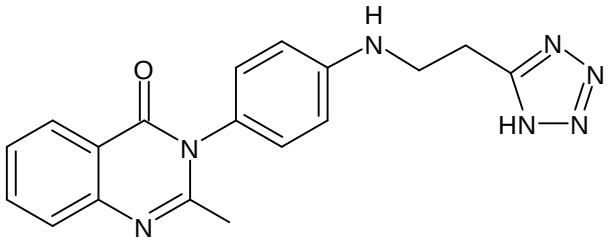
3.2 Antibacterial and antifungal activity

Frolova and colleagues synthesized a novel tetrazole **C** (fig. 3) molecule and evaluated its antibacterial properties. Based on the findings, compound **C** exhibits greater efficacy than ampicillin against every culture that was assessed, with the exception of S. aureus [51]. Tetrazole molecule **D** (fig. 4) was produced by Albalawi , et al., and its antibacterial activity was evaluated by measuring the inhibitory zones by the disc diffusion process [52]. Tetrazole derivatives **E** and **F** (fig. 5) were also created by Cherfi. et al. and then put to the test for antibacterial activity. A moderate degree of activity against the assessed microorganisms was discovered by researchers [53]. Abualnaja et al. synthesized and evaluated many heterocyclic derivative compounds (G, H, I, J and K) for their antibacterial properties. According to the outcomes [54].



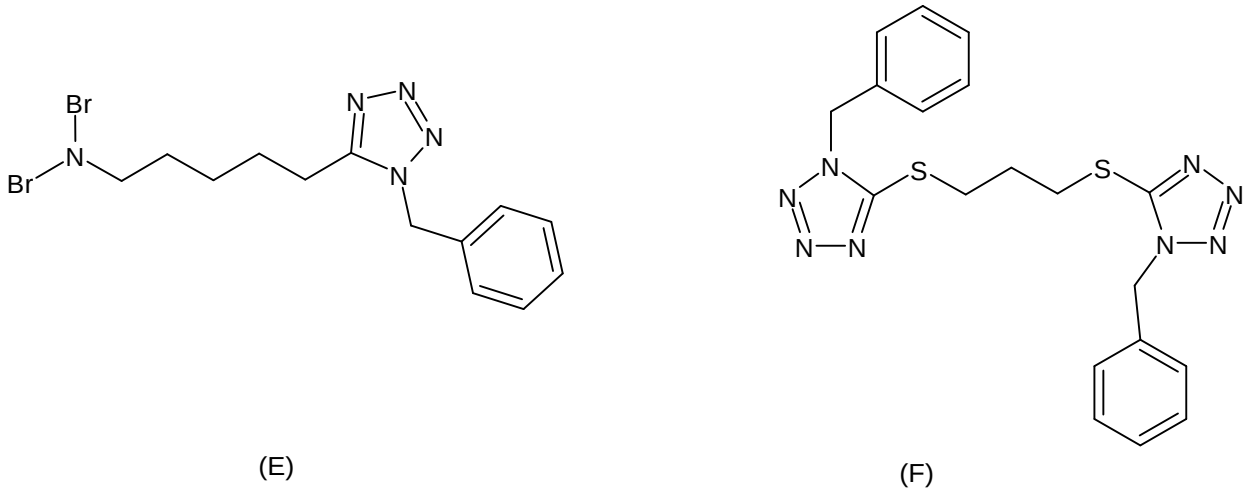
(C)

Figure 3. *Antibacterial acitivitie of Tetrazole Derivatives.*



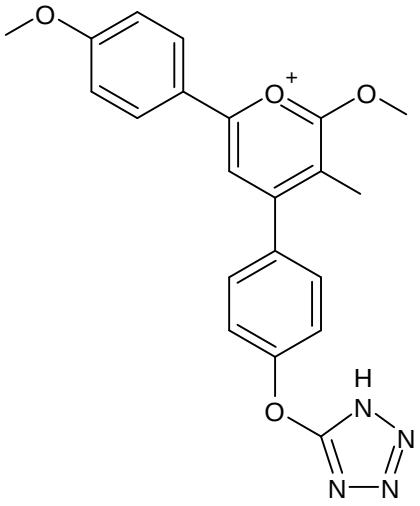
(D)

Figure 4. *Antibacterial acitivitie of Tetrazole Derivatives.*

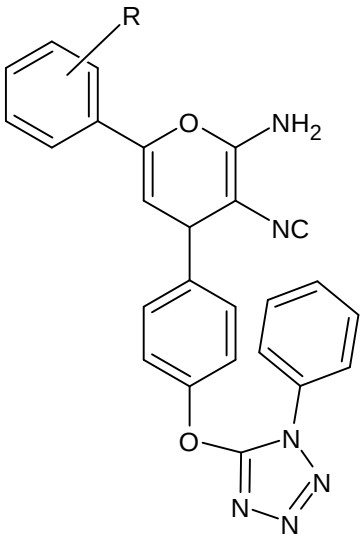


(E) (F)

Figure 5. *Antibacterial acitivitie of Tetrazole Derivatives.*

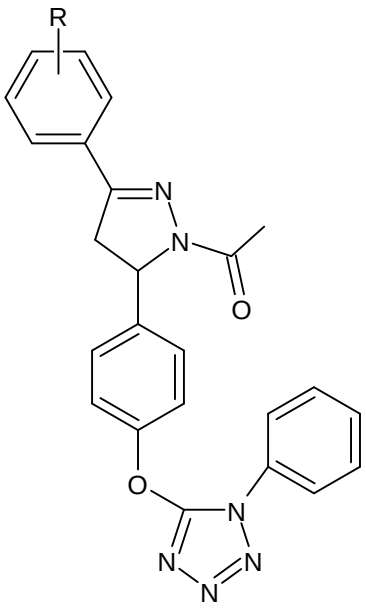


(G)

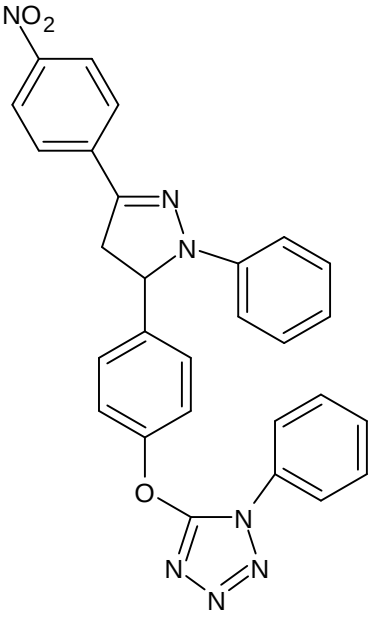


(H) R = 4-OCH_3

(I) R = 4-CH_3



(J) R = 4-Cl

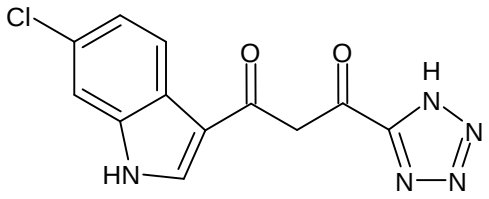


(K)

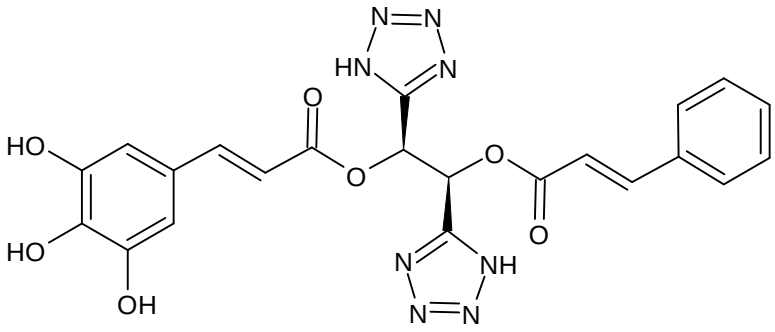
Figure 6. *Antibacterial acitivitie of Tetrazole Derivatives.*

3.3 Antivirals Activity

Tetrazole derivatives have shown significant antiviral activity, making them promising candidates for the development of antiviral agents. These compounds have been found to exhibit inhibitory effects against various viruses such as influenza A (H1N1), HIV, HCV, and others. The unique structure of tetrazoles, acting as bioisosteric analogues of carboxylic acids and amides, contributes to their diverse biological activities, including antiviral properties. Additionally, tetrazole-based molecules have been synthesized and studied for their potential antiviral effects by targeting the RNA polymerase of viruses, highlighting their importance in drug development. Furthermore, the regioselective synthesis of novel tetrazole derivatives has demonstrated moderate inhibitory activity against influenza A virus, showcasing their potential as antiviral agents. Kazar et al. synthesized a tetrazole derivative and examine its activity against HIV virus. The Compound (L and R) were created and examined for their ability to inhibit HIV-1 integrase [55].



(L)

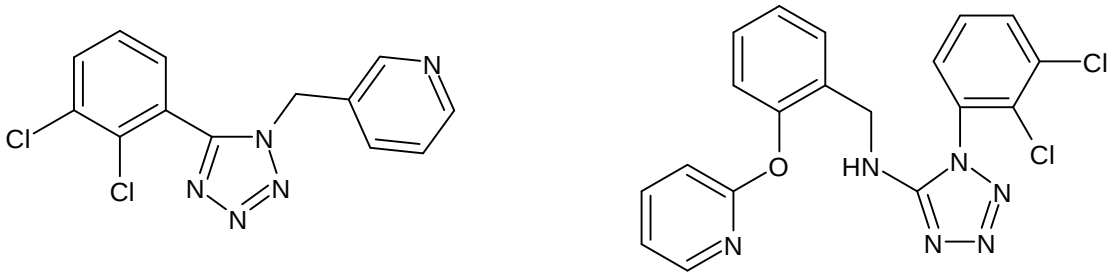


(R)

Figure 7. *Antiviral acitivitie of Tetrazole Derivatives.*

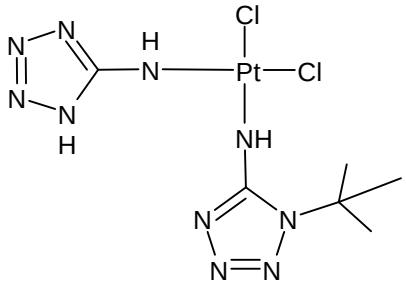
3.4 Anti-inflammatory and analgesic activity

As anti-inflammatory drugs, two types of compounds (M and N) were produced and employed by Jarupula,V. et al. and Albalawi et al. [56]. The tetrazole complexes Pt(II) as complex E and Pd(II) as complex **O** were synthesized by Fan,, Y. L., et al. and evaluated for antineoplastic action. These complexes contained chlorine atoms [57].



(M) (N)

Figure 8. *Anti-inflammatory acitivitie of Tetrazole Derivatives.*



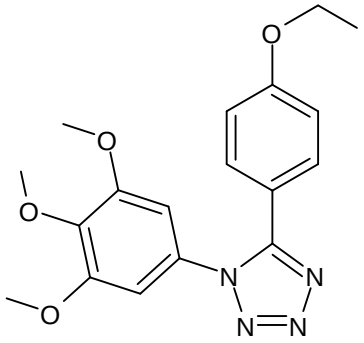
(O)

Figure 9. *Anti-inflammatory acitivitie of Tetrazole Derivatives.*

3.5 Anticancer activity

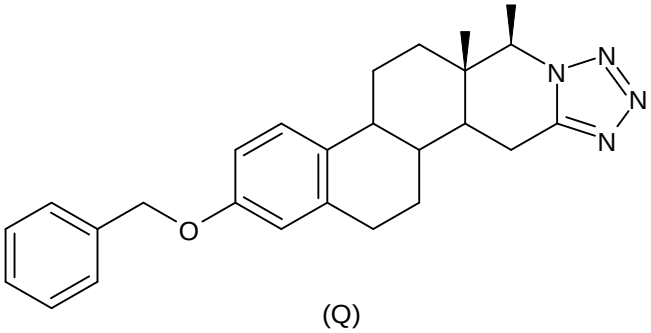
Compound K proved to be more efficient than other compounds against cancer cell lines of the liver carcinoma (Hep G2) and lung adenocarcinoma (A 549) types, according to research conducted by El-Sayed W. A. et al [58]. Compound **P** was produced by Romagnoli R. et al., and

research was done on its anticancer activity against the human liver carcinoma cell line HepG2 [59]. Lastly, the second series of 1,2,3,4-tetrazole chemical was created by Dunga. A.K,. et al. Similar to Compound **P**, a number of the generated compounds prevented the growth of multidrug-resistant cells [60]. Compound **Q** was produced by Lawong, A. et al. and exhibits a significant inhibitory effect on MCF-7 breast cancer cell lines [61].



(P)

Figure 9. *Anticancer acitivitie of Tetrazole Derivatives.*



(Q)

Figure 9. *Anticancer acitivitie of Tetrazole Derivatives.*

3.6 Anti-malarial activity

One of the most common and deadly diseases in the world is malaria, which is often caused by protozoan parasites of the genus Plasmodium, which includes the human malaria parasite species P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi [61]. An estimated 216 million cases of malaria were reported in 2016, an increase of almost 5 million cases over 2015. 445,000

people lost their lives to malaria in the same year, which is comparable to 2015 [62]. P. falciparum, the most deadly human malaria parasite, has the ability to control its genes, which produces strains that are resistant to practically all anti-malarial drugs [63]. There is an urgent need for innovative anti-malarial drugs to overcome drug resistance. Tetrazole derivatives have the potential to be antimalarial agents, hence incorporating tetrazole into quinolone antimalarials may offer promising options against drug-resistant malaria [64].

4. STRUCTURAL MODEFICATIONS

4.1 Substitution Pattern

By applying both the conventional and nucleophilic substitution techniques, a new family of pyrimidine-modified tetrazole and azido derivatives (1–16) was created. Traditional cycloaddition and condensation were used by Saira M., et al. (2020) to create 1H-tetrazol-1-yl)pyrimidine (1-10) compounds. At the same time, conventional and nucleophilic substitution techniques were introduced to create the compounds tetrazolo [1,5-a]pyrimidine (11a, 12a, and 13a), azido-(1H-tetrazol-1-yl) pyrimidine (14a and 15a), and tetrazolo[1,5-c]pyrimidine (16a). The latter method required less processing time and reduced synthesis time. In compounds 11a, 12a, 13a, and 16a, it was discovered that the solvent, temperature, steric effect, electron-donating groups, and electron-withdrawing groups were in charge of directing the azido-tetrazole equilibrium. The single-crystal X-ray diffraction structures of 1, 3, 4, 6, 8, 10, 11a, 12a, 13a, 14a, 15a, and 16a were among the well-characterized produced compounds. Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) were used to study thermal behavior. The synthesis of a new class of pyrimidine-modified tetrazole and azido derivatives is greatly aided by the current work, as evidenced by its straightforward work-ups, safe procedure, good to exceptional yields, and facile reaction approach [65].

4.2 Photolysis of Tetrazoles

By photolyzing biaryl tetrazoles, Chowdhury. A. H, et al. synthesized 9H-Pyrimido[4,5-b] indoles in 2020. They showed that in acidic medium, photolysis of biaryltetrazoles produces good to excellent yields (84–95%) of 9H-pyrimido[4,5-b]indoles [66]. The authors proposed a mechanistic explanation for the reaction, which states that the azide tautomer is produced through photolysis when the tetrazole-azidoazomethine equilibration in acidic medium is shifted

(16 RPR-3000-Å lamp). Molecular nitrogen undergoes photoextrusion in the first photochemical reaction, which yields the equivalent nitrene. Nitrene is then inserted to yield the product. On the other hand, protonation in the extremely acidic trifluoroacetic acid would produce the nitrenium ion, which would most likely be followed by cyclization and proton loss to produce an alternative product. The scientists showed that for the variety of compounds they examined, substituent effects on photolysis are minimal, allowing for the introduction of chemical diversity [67]. Diaziridinones were synthesized in 2020 by Liu and D through photolysis of 1,4-dialkyl-1,4-dihydro-5H-tetrazol-5-ones and 1-alkenyl-4-alkyl-1,4-dihydro-5H-tetrazol-5-ones. They provided an explanation of how 1,4-dimethyl-1,4-dihydro-5H-tetrazol-5-one can be photolyzed to produce diaziridinone [68]. During their examination, the authors found that the thermally very stable tetrazolone could only be photolyzed in ether or 2-propanol, producing secondary compounds solely by radical reactions of the primary photoproducts with the solvent. Nevertheless, a single photoproduct known as 1,2-dimethyldiaziridinone was generated by irradiating the product (degassed samples) in CD3CN at 10−5 Torr using a 150 or 450 W Hg lamp this photoproduct was also identified by 1H-NMR and IR [67].

5. APPLICATIONS OF TETRAZOLE DERIVATIVES

Numerous biological applications, including antibacterial, anti-inflammatory, antifungal, antiviral, antitubercolous, cyclo-oxygenase inhibitors, antinociceptive, hypoglycemic, and anticancer properties, are known for tetrazoles and their derivatives. They serve as nanocatalysts as well [83].

5.1 Drug Development

Tetrazoles are a crucial component with a variety of uses in the pharmaceutical and material sciences, information recording systems, photography, and coordination chemistry as attractive ligands [84]. Since tetrazole is metabolically resistant against many of the biological alterations that carboxylic acid's functionality is prone to in the liver, it is typically utilized as the bioisoster of carboxylic acid [87]. Tetrazole has the ability to replace carboxylic acid in medications, which may boost the drug's lipophilicity and bioavailability while lowering its negative effects. Several prodrug strategies have been used to improve the oral bioavailability of tetrazole pharmaceuticals [88]. Tetrazole can also interact noncovalently with biological targets in a variety of ways, and

its derivatives have a wide range of pharmacological properties, including anti-inflammatory [89], anti-angiogenic [90], antibacterial [91], anticancer [92], antifungal [93], antimalarial [94], antitubercular [95], and antiviral [96] properties. Notably, tetrazole derivatives as pharmacologically relevant scaffolds have attracted a lot of interest recently. Tetrazole-based medications, such as cefamandole, ceftezole, losartan, and valsartan, have already been utilized in clinics for the treatment of various disorders.

The majority of infections in hospital and community settings, including bloodstream infections, pneumonia, wound infections, and STDs, are caused by bacteria, and they continue to be one of the leading causes of morbidity and mortality worldwide [97]. Antibiotics are frequently used to treat bacterial infections, and the presence of tetrazole skeleton in several therapeutically utilized antibacterial medicines suggests that tetrazole derivatives may also have antibacterial potential. In a work conducted by Herr et al. [85], eight distinct derivatives of substituted 5-phenyl-1-(5-substituted phenyl)-4, 5-dihydro-1H-pyrazol-3-yl)-1H-tetrazole (4a-h) were produced through a reaction between the chalcones and hydrazine hydrate in the presence of glacial acetic acid. In a similar vein, Kushwaha et al [86] synthesis and assessment of several 1-substituted tetrazole derivatives as antibacterial agents. The antibacterial and antifungal properties of a number of newly developed 1-substituted tetrazole derivatives were investigated.

First-generation cephalosporin antibiotic ceftezole and second-generation cephalosporin antibiotic cefamandole, also referred to as cephamandole, both have broad-spectrum antibacterial activity against both Gram-positive and Gram-negative organisms, even in drug-resistant pathogens. They also have the ability to inhibit the synthesis of bacterial cell walls. An oxazolidinone-class antibiotic prodrug called tedizolid (second-generation oxazolidinone) has already been licensed to treat acute bacterial skin and skin structure infections brought on by susceptible isolates of various Gram-positive bacteria. Tedizolid's antibacterial action is accomplished by binding to the bacterial ribosome's 50S subunit, which inhibits the production of new proteins. Tedizolid exhibits a distinct method of action in comparison to other antibacterial medicines of the nonoxazolidinone class, hence rendering it susceptible to certain resistance mechanisms [34]. Letrozole, a tetrazole derivative, has already been used in clinics to treat some forms of breast cancer, typically following resection and tamoxifen's failure.

Nonsteroidal aromatase inhibitors like letrozole work by competitively and reversibly binding to the heme of the cytochrome P450 unit of aromatase to stop it from generating estrogens [35].

In addition to their outstanding ability to combat germs, cancer, fungal infections, and hypertension, tetrazoles demonstrated encouraging in vivo and in vitro actions against Alzheimer's disease, asthma, malaria, tuberculosis, and viruses. Some of them showed promising in vitro and in vivo activity against drug-resistant, including multidrug-resistant and extensively drug-resistant pathogens, in addition to their strong activity against drug-sensitive organisms. Furthermore, a number of them—including the leukotriene antagonist tomelukast (LY171883)—have already been applied in clinical settings and have demonstrated potential efficacy against Alzheimer's disease [18].

5.2 Tetrazole-based (nano) catalysts

This part provides an overview of the (nano)materials based on tetrazole that have been investigated as heterogeneous catalysts with high catalytic activity for environmental applications in recent years, such as the degradation of organic dyes and nitroarenes as toxic and hazardous pollutants.

Nitro compounds are among the most significant contaminants in water. There are a few methods for removing these substances from water, but the catalytic reduction of these chemicals is the most significant and useful. Researchers used various heterogeneous catalysts in their experiment [69-72]. The preparation of these catalysts can be done on a variety of substrates, such as silica [76, 77], synthetic or natural polymers [75], and Fe_3O_4@SiO_2 [73, 74]. Nasrollahzadeh et al. stated in 2019 that they had created an effective and heterogeneous catalyst by immobilizing the ((1-phenyl-1H-tetrazole-5-thiol) Pd(II)) complex on Fe_3O_4@SiO_2 via a simple technique [78]. Fe_3O_4@SiO_2-Tet-thio-Pd(II) is a new catalytic system that demonstrated remarkable efficiency in reducing 4-nitro phenol (4-NP) to 4-aminophenol (4-AP) and Cr(VI) to Cr(III) in water. With great efficiency, the catalyst might be utilized five more times.

Apart from nitro and Cr(VI) compounds, other chemicals that pollute water include potassium hexacyanoferrate (III) ($K_3[Fe(CN)_6]$) and nigrosin (NS). In order to create magnetic Pd(II) nanocatalyst, Sajjadi et al. effectively identified an innovative and efficient method [79]. The extremely magnetically active catalyst Fe_3O_4@SiO_2-Thiotet-Pd(II) was produced and utilized to

degrade various contaminants in water, including NS, 4-NP, $K_3Fe(CN)_6$, and Cr(VI). With regard to Escherichia coli, the catalyst exhibited antibacterial activity. By using magnetic decantation, the catalyst can be recycled and utilized again eight times. Nasrollahzadeh et al. successfully disclosed a novel approach in another work conducted in 2019 to create Pd(II)-tetrazole complex decorated on silica covered Fe_3O_4 NPs (Fe_3O_4@SiO_2-Tet-Pd(II)) [80]. They adorned the Fe_3O_4@SiO_2 surface with 5-phenyl-1H-tetrazole, a suitable ligand. NaBH4 was used to reduce Cr(VI), 4-NP, and 2,4-dinitro phenylhydrazine (2,4-DNPH) utilizing the produced nanocomplex. Five cycles of high efficiency reusability are possible for the synthesized catalyst.

Synthetic pigments and organic dyes are among the numerous pollutants that have entered the environment as a result of the growth of the food processing, cosmetic, printing, paper, and ceramics industries. Eliminating methylene blue (MB) from the environment is especially crucial because it is one of the most significant organic pigments [81]. By concentrating the Cu(II)-5-phenyl-1H-tetrazole complex on the surface of Fe_3O_4@SiO_2 NPs (Fe_3O_4@SiO_2-Tet-Cu(II)) in 2018, Nasrollahzadeh et al. were able to successfully develop a novel catalyst [82]. By using $NaBH_4$ as the reductant, the synthesized catalyst was used in the reduction process of 2,4-DNPH to 2,4-diaminophenylhydrazine (2,4-DAPH), Nigrosin (NS), MB, and 4-NP in water at room temperature. Fe_3O_4@SiO_2-Tet-Cu(II) has a high efficiency and can be reused five times.

6. CONCLUSION

In summary, this review have discussed about the recent progresses in the synthesis of different kind of tetrazole derivatives such as mono-substituted, 1,5H-disubstuted and 2,5H-disubstituted tetrazoles. These tetrazole derivatives are also found to have both biological and clinical applications as it is being described by various scientific researches such as antiviral, antituberclosis, anticancer, antimalarial and antiinflamentary activity.

Future research must address a number of issues, including the use of tetrazoles as efficient ligands to create a variety of ionic liquids and highly energetic compounds, the creation of novel methods for the synthesis of tetrazole and its derivatives, the creation of tetrazole derivatives

with exceptional catalytic activity, the development and use of biowastes as natural supports in the design of tetrazole derivatives on them, the use of natural supports for the immobilization of various tetrazoles with superior catalytic activity, and the creation of magnetic tetrazole derivatives or complexes with exceptional catalytic competence.

DECLARATION

All the authors have decleared no any financial conflict of interest.

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