Chapter 4

A Click Chemistry Approach to Tetrazoles: Recent Advances

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Additional information is available at the end of the chapter

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Abstract

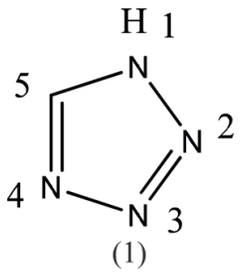
Introduction to tetrazole and click chemistry approaches was briefed in a concise way in order to help the readers have a basic understanding. Tetrazole and its derivatives play very important role in medicinal and pharmaceutical applications. The synthesis of tetrazole derivatives can be approached in ecofriendly approaches such as the use of water as solvent, moderate conditions, nontoxic, easy extractions, easy setup, low cost, etc. with good to excellent yields.

Keywords: click chemistry, tetrazoles, biological activity, synthesis and molecular docking

1. Introduction

1.1. Chemistry of tetrazoles

1*H*-Tetrazole (**1**) is a crystalline light yellow powder and odorless. Tetrazole shows melting point temperature at 155–157°C. On heating, tetrazoles decomposed and emit toxic nitrogen fumes. These are burst vigorously on exposed to shock, fire, and heat on friction.



(1)

Tetrazoles easily react with acidic materials and strong oxidizers (acidic chloride, anhydrides, and strong acids) to liberate corrosive and toxic gases and heat. It undergoes reaction with few active metals and produces new compounds which are explosives to shocks. It involves exothermic reactions with reducing agents. On heating or burning, it releases carbon monoxide, carbon dioxide, and harmful nitrogen oxide. Tetrazole dissolves in water, acetonitrile, etc. Generally, dilute 1*H*-tetrazole in acetonitrile is used for DNA synthesis in biochemistry.

The presence of free N-H causes the acidic nature of tetrazoles and forms both aliphatic and aromatic heterocyclic compounds. Heterocycles of tetrazoles can stabilize the negative charge by delocalization and show corresponding carboxylic acid pKa values. Tetrazole nitrogen electron density results in the formation of so many stable metallic compounds and molecular complexes. This compound shows strong negative inductive effect (−I electron withdrawing) and weak positive mesomeric effect (+M electron releasing).

The tetrazole is a five-membered aza compound with 6π electrons, and 5-substituted tetrazole reactivity is similar to aromatic compounds. The Huckel 6π electrons are satisfied by four π electrons of ring and one loan pair of electrons of nitrogen. The acidic nature of tetrazole is similar to corresponding carboxylic acids, but there is a difference in annular tautomerism of ring tetrazoles to carboxylic acids. The acidic nature of tetrazole is mainly affected by substitution compound nature at C-5 position. 5-Phenyltetrazole anion shows high acidic nature like benzoate due to resonance stabilization. A simple method to produce tetrazole anion is the reaction of tetrazole with metal hydroxides and can be stable in aqueous and alcoholic solution at high temperature.

1.2. Introduction to click chemistry

Click chemistry is called as tagging in synthesis of chemicals. It is in the category of non-harmful reactions, proposed initially to unite the base materials of choice with certain bimolecular substance. It also can be termed as a non-peculiar reactive process. Indeed it explains a way of generating products that follow examples in nature. At the same time, it can produce the variety of materials by consolidating small compatible units. Usually, click reactions join a biomolecule and a reporter molecule. Click chemistry is not limited to the state of survival. It is the concept of a "click" reaction that has been used in pharmacological and various biomedical applications. It also can be described as non-single specific reaction etic application. Nevertheless, it is observed to be highly functional in the diagnosis of localization and qualification of bimolecular material.

Click reactions occur in one pot and generally make an evidence of being uninterrupted by water. They produce negligible and innocuous corollary and are spring-loaded. In addition to this, they are distinguished by a high thermodynamic driving force that pushes them rapidly and irrevocably to supply a single reaction product, with high reaction specificity. In few cases, they are created with both regio- and stereospecificity. These click reactions are specifically adaptable in the case of segregating and navigating the molecules in composite biological environments. In such conditions, items in like manner should be physiologically steady, and any side effects should be nonlethal.

Researchers have opened up the likelihood of hitting specific focuses in complex cell lysates, by developing specific and controllable bio-orthogonal reactions. Recently, they have adjusted snap science for use in live cells, for instance, utilizing little atom tests that find and append to their objectives by click reactions. In spite of difficulties of cell porousness, bio-orthogonality, foundation naming, and response effectiveness, click responses have officially demonstrated valuable in another era of pull-down tests and fluorescence spectrometry. All the more as of late, novel strategies have been utilized to fuse click response accomplices onto and into biomolecules, including the joining of unnatural amino acids containing receptive gatherings into proteins and the change of nucleotides. These strategies speak to a piece of the field of compound science, in which click science assumes a central part by deliberately and particularly coupling secluded units to different finishes.

This refresh outlines the developing use of "click" science in various zones, for example, bioconjugation, sedate disclosure, materials science, and radiochemistry. It additionally talks about snap science responses that continue quickly with high selectivity, specificity, and yield. Two essential qualities make click science so appealing for collecting mixes, reagents, and biomolecules for preclinical and clinical applications. To begin with, click reactions are bio-orthogonal. First of all, they are neither reciprocal nor their functional gatherings of different products connect with functionalized biomolecules. Secondly, the responses continue effortlessly under gentle nontoxic conditions. Example is their reaction at the room temperature and, for the most part, in water. The copper-catalyzed Huisgen cycloaddition, azide-alkyne [3+2] dipolar cycloaddition, Staudinger ligation, and azide-phosphine ligation all have these interesting qualities. These responses can be utilized to change one cell part while leaving others unharmed or untouched.

Click chemistry has discovered expanding applications in all parts of medication revelation in restorative science, for example, for producing lead mixes through combinatorial strategies. Through bioconjugation click chemistry is thoroughly utilized in proteomics and nucleic exploration. In radiochemistry, specific radiolabeling of biomolecules in cells and living creatures for imaging and treatment has been acknowledged by this innovation. Bifunctional chelating operators for a few radionuclides are valuable for positron discharge tomography and single-photon emanation processed tomography. They have additionally been set up by click chemistry. This survey reasons that click chemistry is not the ideal conjugation, and gathering innovation for all applications, however, gives a capable, appealing another option to ordinary science. This science has turned out to be prevalent in fulfilling numerous criteria, e.g., biocompatibility, selectivity, yield, stereospecificity, etc. In this way, one can expect that it will subsequently turn into a more normal procedure soon for an extensive variety of uses.

1.3. Introduction to molecular docking

Molecular docking (hereafter, MD) is the study of fitting together by two or more molecular components (e.g., drug and enzyme or protein). It is something like a problem of "lock and key" (**Figure 1**). It is an optimization issue which clearly explains how best a ligand and protein bind based on orientation. As both ligand and protein are flexible, a "hand-in-glove"

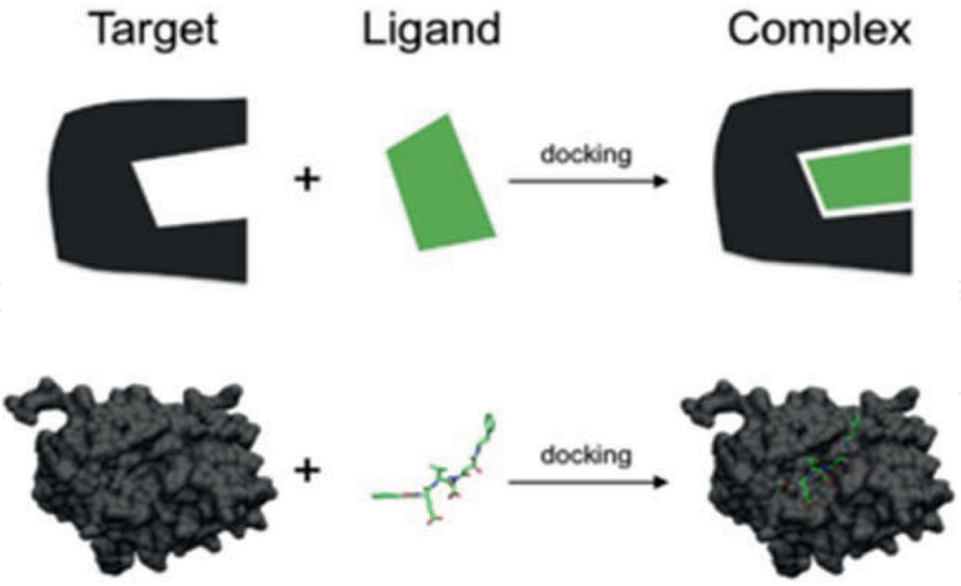


Figure 1. Lock and key models for Ligand-Target fitting.

word suit more effective compared to "lock and key" model. Both ligand and protein adapt their confirmation for overall binding, known as "induced effect."

MD research depends mostly on computationally simulating the molecular recognition process by decreasing the free energy of overall system. Basic awareness on the preferred orientation in turn may be used to predict the binding affinity between two molecules used. Molecular docking is an invaluable tool in the field of molecular biology, computational structural biology, computer-aided drug designing, and pharmacogenomics.

There are two ways of docking approaches, namely, the first matching methodology which explains ligand-enzyme as complementary surfaces and the other simulated docking methodology of protein and ligand pairwise interaction energies. The application of docking in a targeted drug-delivery system is a huge benefit. One can study the size, shape, charge distribution, polarity, hydrogen bonding, and hydrophobic interactions of both ligand (drug) and receptor (target site).

1.4. Aims and significance

The investigation of tetrazoles centers the most imperative organic exercises like antihypertensive, against inflammatory, antibacterial, antifungal, anticancer, antidiabetic, and hypoglycemic activity. Different strategies for synthesis and characterization techniques were discussed.

Throughout the previous couple of years, investigation of tetrazole chemistry has been rapidly expanded in view of its huge applications, for the most part because of the pretended by this heterocyclic usefulness in restorative chemistry. This provides more support to pharma field and metabolically stable swap for carboxylic acid functionalities, particularly, joining of the tetrazole exercises into angiotensin II rival structures, sartans (2–4) [1–4].

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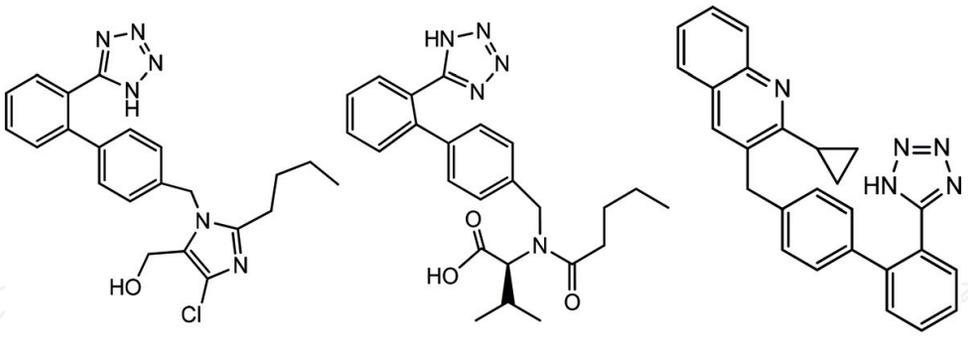
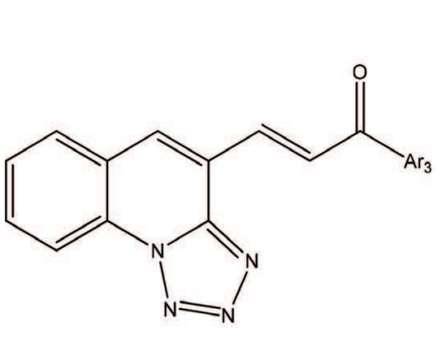


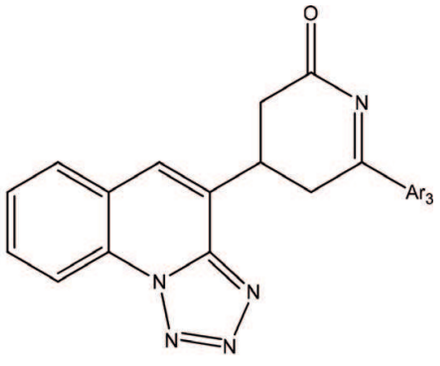
LOSARTAN (2) VALSARTAN (3) BMS-183920 (4)

Irbesartan (5), one of the essential tetrazole subsidiaries, has a place with the sort of medication called angiotensin II receptor enemy antihypertensives. This medication is utilized for the treatment of high blood pressure (hypertension) and for kidney issues because of Type 2 diabetes (noninsulin-dependent).

Tetrazolo quinoline has an imminent and empowering new structure for the novel against the anti-inflammatory (6) and antibacterial (7) agents [3, 4].

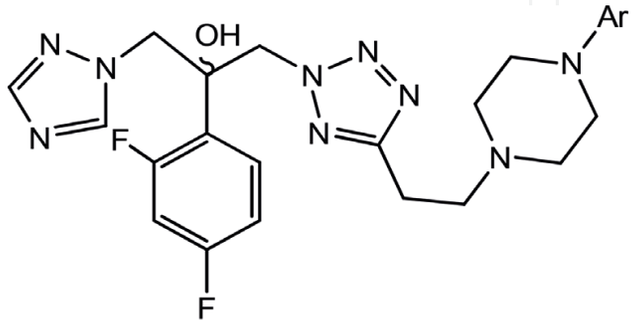


$Ar_3 = C_6H_5$, p-BrC_6H_4, p-ClC_6H_4
(6)



$Ar_3 = C_6H_5$, p-BrC_6H_4, p-ClC_6H_4
(7)

Piperidine-substituted tetrazoles (**8**) showed antifungal activity.



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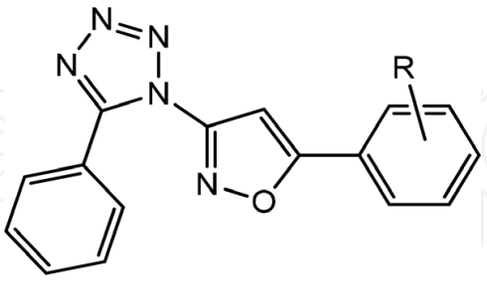
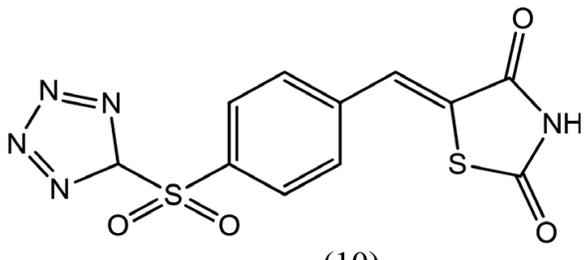
Tetrazole derivatives (**9**) have been chosen and enhanced for their anticancer action on the majority of various human tumor cell lines separated from nine neoplastic disease sorts. The capable anticancer compound was observed to be dynamic with specific impact on ovarian cancer [1–4].



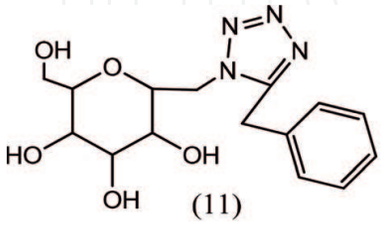
(9)

The 2,4 thiazolidinedione by-products (**10**) comprise tetrazole loop for their antidiabetic movement. The greater part of the mixes indicated great antidiabetic action when contrasted to glibenclamide [1–4].



(10)

The in vivo hypoglycemic action of tetrazole bears *N*-glycosides as SGLT2 inhibitors. A progression of 5-[(5-aryl-1*H*-pyrazol-3-yl)methyl]-1*H*-tetrazoles (**11–13**) has been assessed for their in vivo antihyperglycemic action. A portion of the mixture have indicated critical glucose bringing down the movement [1–4].



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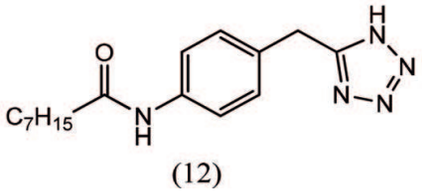

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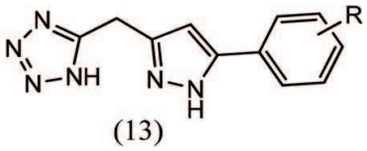

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1.5. Motivation of the chapter

Powerful drugs in opposition to hypertension, cancer, and bacterial and fungal infections have to fulfill a number of requirements like toxicity to tumor cells and are capable of being

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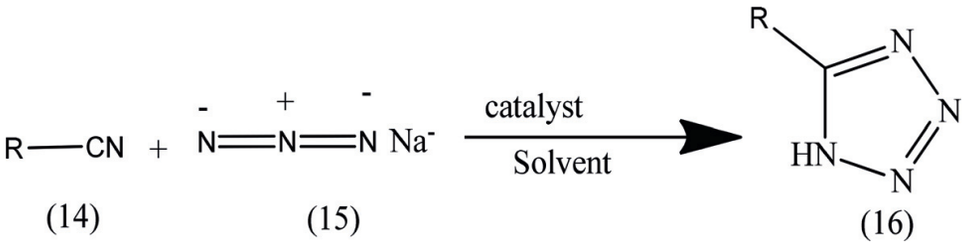
dissolved for efficient delivery. This makes necessary full-fledged characterization of drug position, comprising achieved synthetic strategies. In this chapter we directed on tetrazole biological activities. As a consequence, the need of synthetic routes to prepare tetrazole derivatives that are selective toward specific malfunctioning enzyme connects with illness. The study of good approaches of tetrazoles and medicinal applications will definitely allow to propose more useful drugs.

1.6. History of tetrazoles

Since 1901, regular synthesis of 5-switched-1*H*-tetrazoles (16) has been accounted for to continuation of [3+2] cycloaddition of azide (**14**) with nitriles (**15**). This strategy experiences various disadvantages including utilization of costly and poisonous metal natural azide, exceedingly dampness touchy response conditions, solid Lewis corrosive, and hydrazoic corrosive. The "click" chemistry approach using metal catalysis in fluid arrangement is an outstanding evolution over last strategies, however every so often still requires the monotonous and tedious expulsion of metal salts from the acidic items.



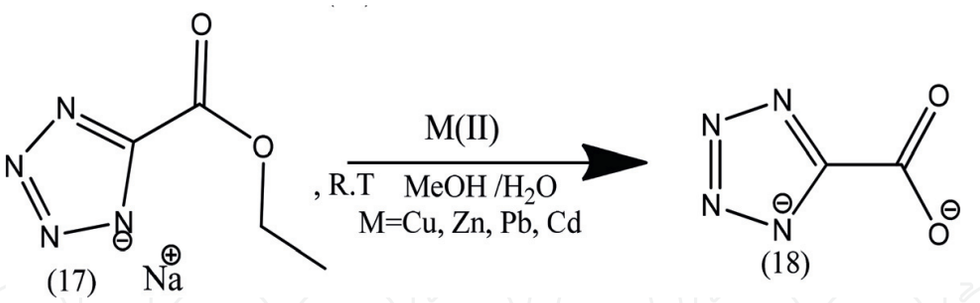
Tetrazoles as a gathering of heterocyclic compounds are accounted for having an expansive range of organic exercises, for example, antibacterial, antifungal, antiviral, pain-relieving, mitigating, antiulcer, and antihypertensive exercises. Likewise, 5-substituted-1*H*-tetrazoles can work as lipophilic spacers and carboxylic corrosive surrogates, forte explosives and data recording frameworks in materials ligands, and forerunners of an assortment of nitrogen-containing heterocycles in coordination science.

2. Synthesis of tetrazole and its analogues

2.1. Synthesis and crystal structures of copper(II), zinc(II), lead(II), and cadmium(II)

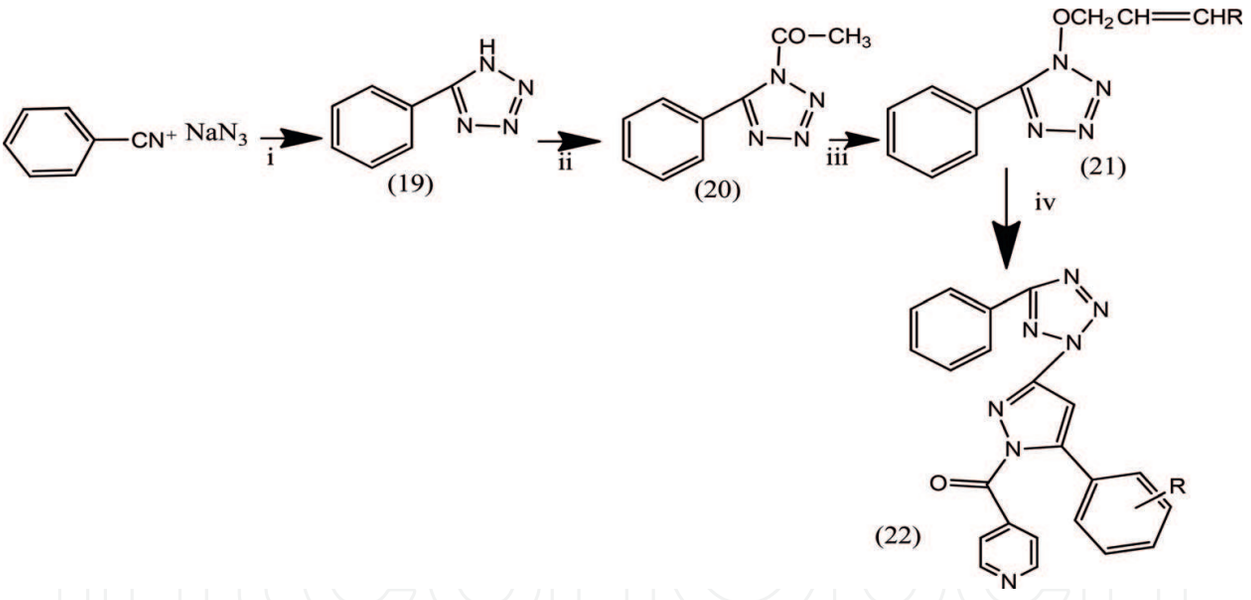
2.1.1. Tetrazole-5-carboxylate mixtures produced via in situ hydrolysis reaction

A facile method to synthesize Cu(II), Zn(II), Pb(II), and Cd(II) complexes with di-anionic tetrazole-5-carboxylate (ttzCOO2−) ligands (18), involving an in situ hydrolysis of 1*H*-tetrazole-5-carboxylic acid ethyl ester sodium salt (17) was described [5–8].



2.2. Synthesis, characterization, and anti-inflammatory activity of novel *N*-substituted tetrazoles

5-Phenyl tetrazole (**19**) responds with acidic anhydride to produce 5-phenyl 1-acetyl tetrazole (**20**), which can be additionally served with various electronically or structurally divergent aldehydes to shape chalcones (**21**). Chalcones additionally respond with isonicotinic acid hydrazide to produce pyrazolines (**22**) [9–12].



Reagent conditions: (i) DMF/ammonium chloride; (ii) acetic anhydride, 20 min; (iii) R-CHO, 50% KOH, ethanol; (iv) isonicotinic acid hydrazide/GAA.

2.3. Synthesis of 5-substituted 1*H*-Tetrazole using nano-ZnO/Co_3O_4 catalyst

5-Phenyl, 1*H*-tetrazole (24) is synthesized by reacting 1 mmol benzonitrile (23) and 1.5 mmol NaN_3 in the presence of nano-ZnO/Co_3O_4 catalyst and 3 mL DMF for 12 h at 120–130°C [13–16].

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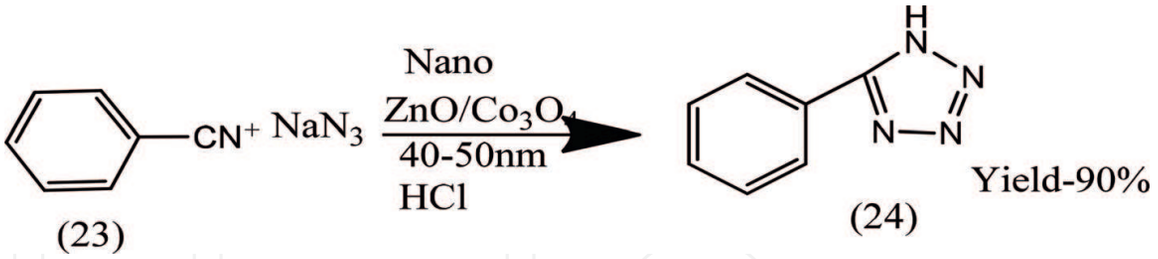
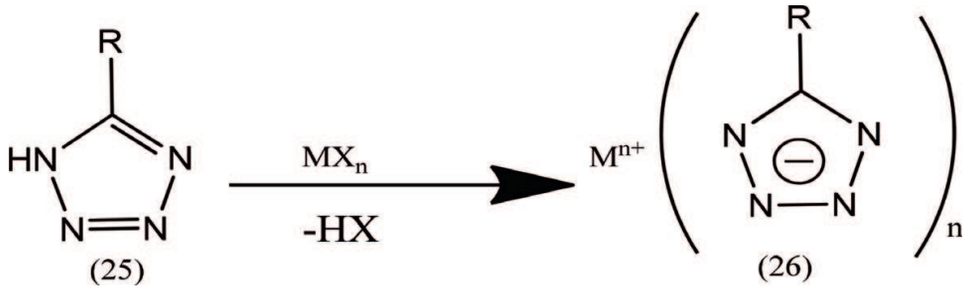


2.4. Advances in the synthesis of tetrazoles coordinated to metal ions

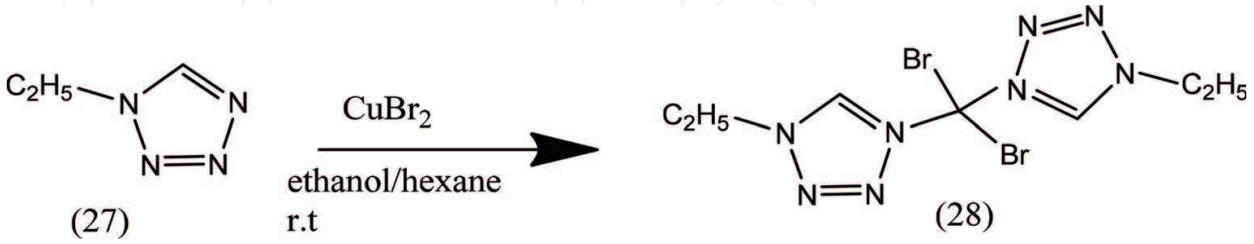
2.4.1. Reactions of tetrazoles with metal bases and salts

Tetrazoles (**25**) react with metal bases or salts to synthesize tetrazole-containing metal derivatives (**26**) [17–21].



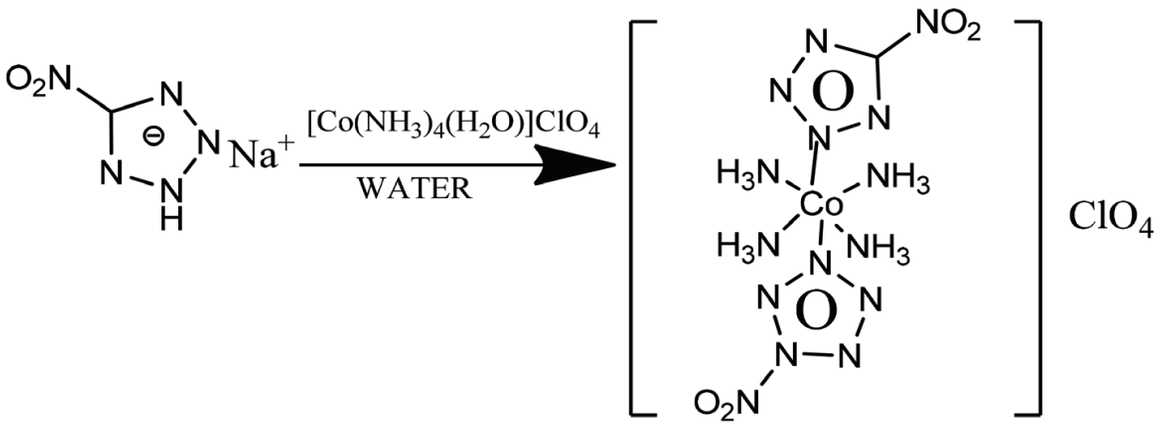
2.4.2. Responses of N1-substituted tetrazoles with metal salts

N1-substituted tetrazoles (**27**) due to the absence of the labile hydrogen iota in the ring, so they don't display acidic properties. In this way, the N1- and N2-substituted tetrazoles (**28**) are associated with the development of metal subsidiaries only in the unbiased frame [22, 23].



2.4.3. Substitution of ligands for tetrazoles in coordination compounds

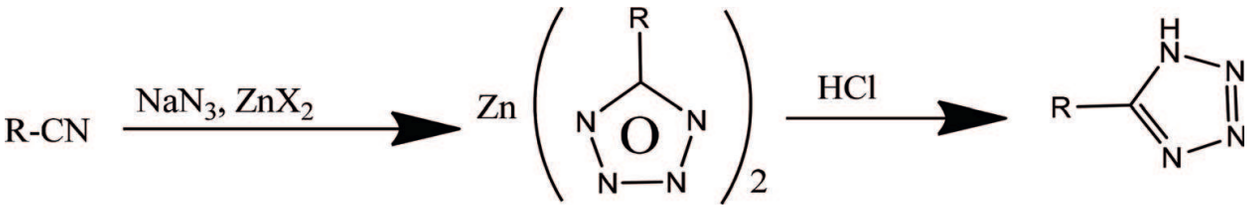
To synthesize tetrazole-containing complexes with anionic ligands (29), tetrazole reacts with another ligand in a coordination compound [24, 25].



(29)

2.4.4. Metal-promoted cycle formation

The synthetic protocol involves reaction of inorganic azides and organic nitriles in the presence of Zn(II) salts under hydrothermal conditions to afford 5-substituted-1*H*-tetrazoles via 1,3-dipolar cycloaddition [26].



2.5. Synthesis of chosen 5-thio-substituted tetrazole subordinates and assessment of their antimicrobial exercises

To union of 5-thio replaced tetrazole subordinates and assessment of their antibacterial and antifungal properties, industrially accessible benzyl isothiocyanate (**30**) and sodium azide respond in presence of water to create 1-benzyl-1*H*-tetrazole-5-thiol (**31**) in great yield. The untouched mix is served with 1,3-dibromopropane with tetrahydrofuran to give a moderate 1-benzyl-5-[(3-bromopropyl)thio]-1*H*-tetrazole (**32**). The synthon is another compound and revealed here for the first time. This compound is treated with relating amines or thiols to manage the cost of the 5-thio-substituted tetrazole derivatives (**33**) [27–31].

2.6. Synthesis of novel 1*H*-tetrazoles: spectral characterization and antibacterial activities

The tetrazoles (35, 37) were orchestrated in outstanding reactiveness by the response of sodium azide and triethyl orthoformate with relating amines, viz., 1-[3-(2-amino ethyl)-1*H*-

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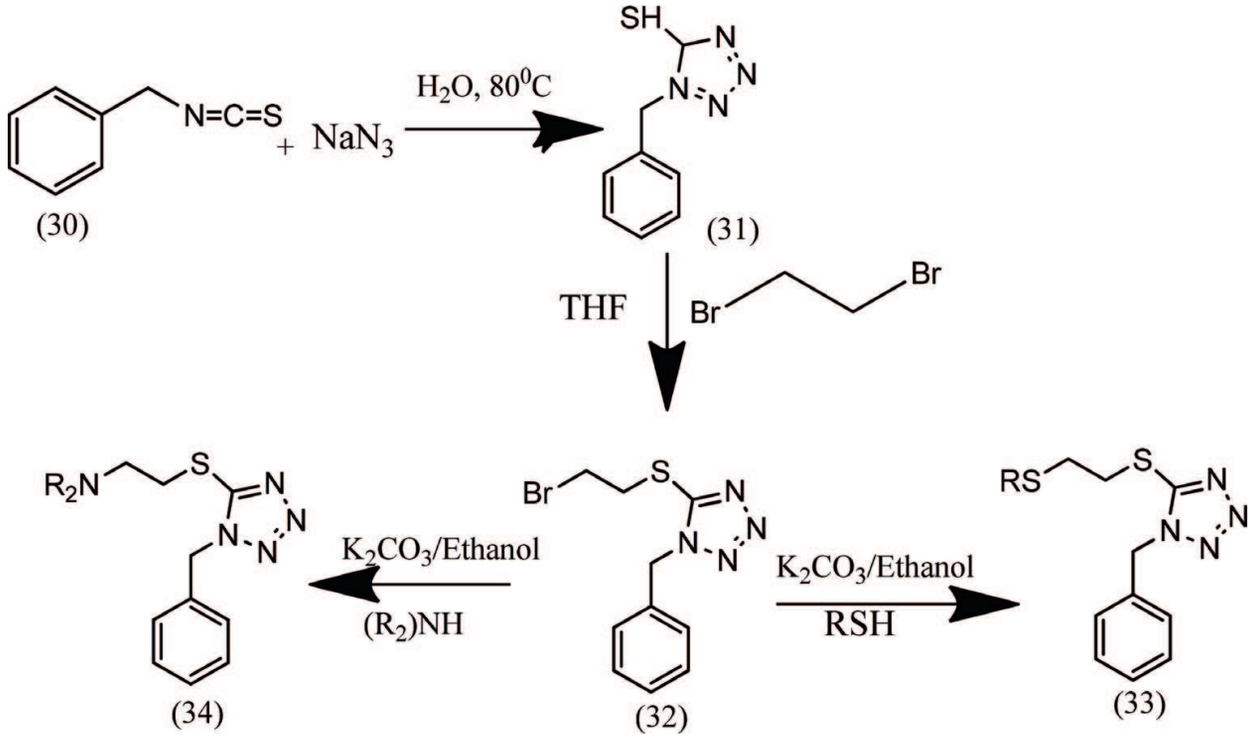
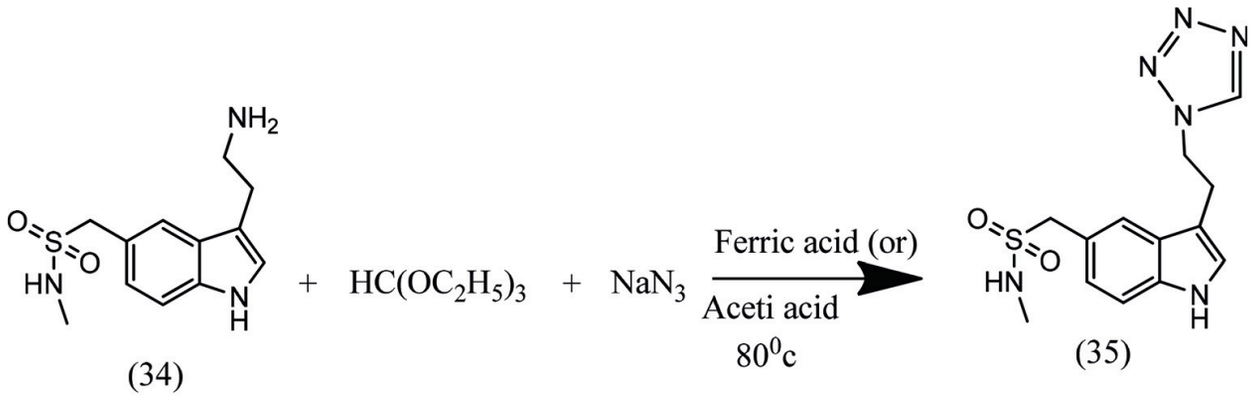
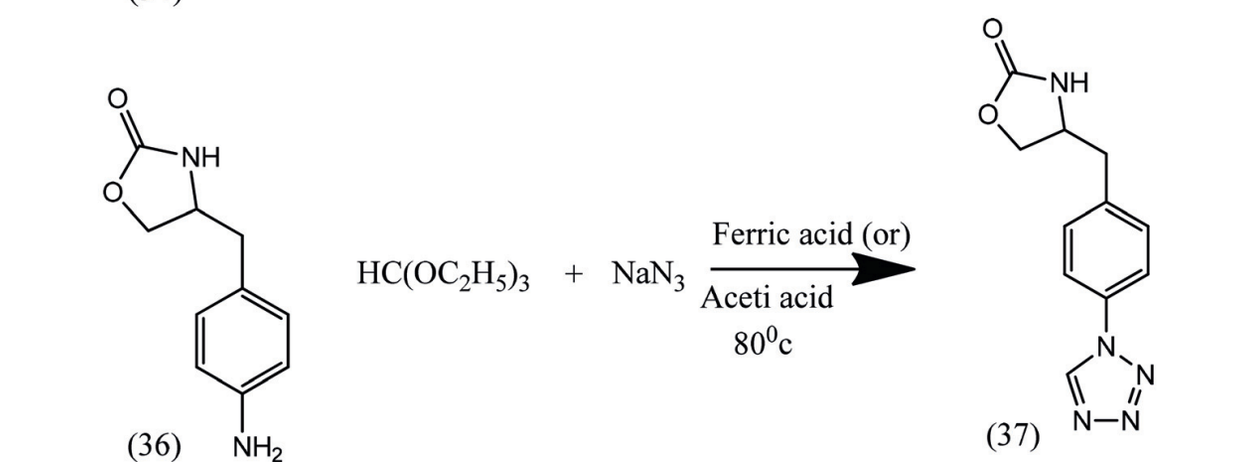


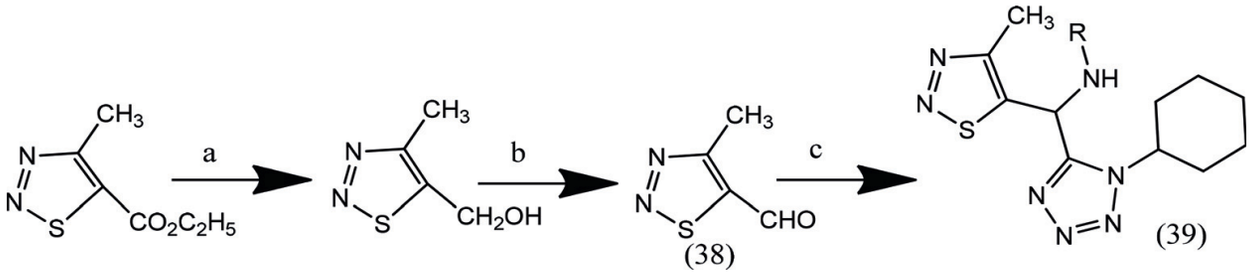




indol-5-yl]-*N*-methyl methanesulfonamide (**34**) or 4-(4-aminobenzyl)-1,3-oxazolidin-2-one (**36**) in acidic corrosive or formic corrosive [32–36].

2.7. Synthesis of tetrazole-containing 1,2,3-thiadiazole subordinates through U-4CR and their opposition of TMV movement

To prepare tetrazole-containing 1,2,3-thiadiazole derivative (**39**), take 4-methyl-1,2,3-thiadiazole-5-carbaldehyde (**38**), and substituted amine is mixed in methanol at room temperature. The imine was precondensated for 0.5–1 h, and afterward cyclohexyl isocyanide and TMSN3 were included. The response blend was mixed for 12–24 h at room temperature until the point when the response was finished (demonstrated by TLC). At that point the natural dissolvable was dissipated in vacuum. The unrefined items were decontaminated by a silica gel segment utilizing ethyl acetic acid derivation/oil ether (1:2–1:3 (v/v), 60–90°C) as an eluent to give the corresponding products as white or light yellow solids in direct yields [37–41].



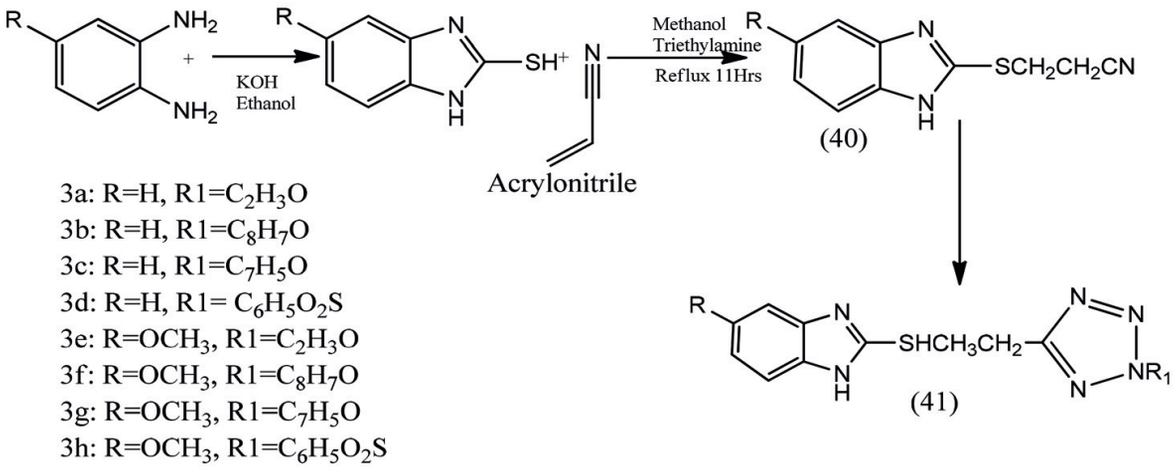
Reagents and conditions: (a) $NaBH_4$ (2.0 equiv.), EtOH, 0°C for 1 h, r.t. for 6 h; (b) pyridinium chlorochromate (2.0 equiv.), CH_2Cl_2, r.t. for 8 h; (c) (i) R-NH2 (1.0 equiv.), CH_3OH, r.t. for 0.5–1 h; and (ii) cyclohexyl isocyanide (1.2 equiv.), $TMSN_3$ (1.5 equiv.), r.t. for 12–24 h.

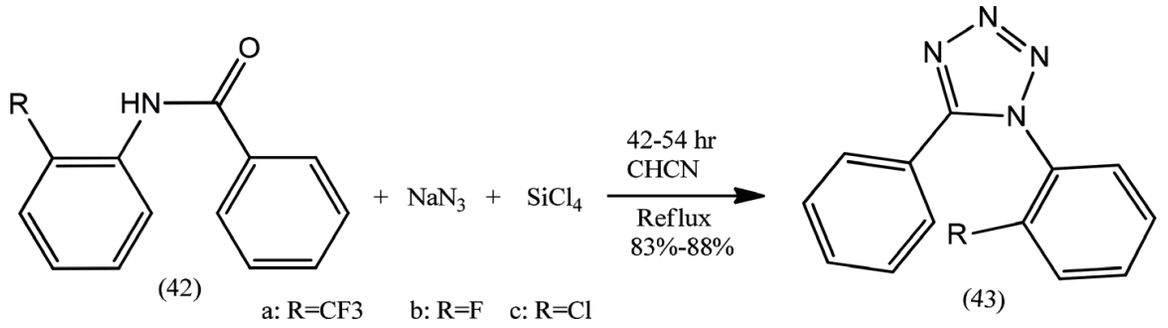
2.8. Synthesis of 2-{[2-(1*H*-tetrazole-5-yl)ethyl]sulfanyl}-1,3-benzimidazole (3) as antioxidants

10 mmol of 3-(1,3-benzimidazole-2-yl-sulfanyl)propanenitrile, 10 mmol sodium azide (**40**), 10 mL of DMF, and 10 mmol of zinc chloride were accepted in a flask, and the substances were warmed in an oil bath for 6 h at 125°C. After the routine workup, it was recrystallized from equimolar DMF-ethanol blend to get compound (**41**) [42, 43].

2.9. Single-leap synthesis of sterically hindered b1,5-disubstituted tetrazoles from bulky secondary *N*-benzoyl amides: usage of triazidochlorosilane (TACS)

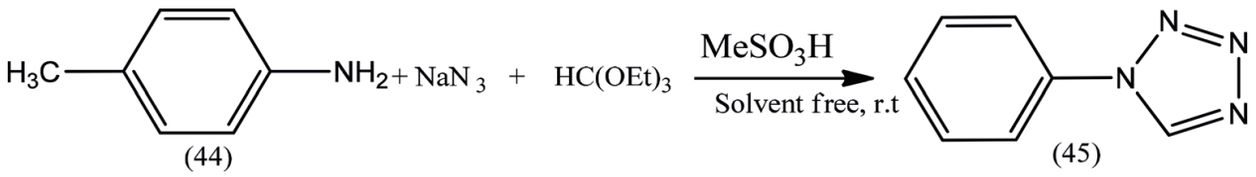
A mixture of 1-(2-trifluoromethane phenyl)-5-phenyl-1*H*-tetrazole (**42**), sodium azide, and tetrachlorosilane in dry acetonitrile was refluxed under dry conditions to give the corresponding tetrazole **43** [44, 45].



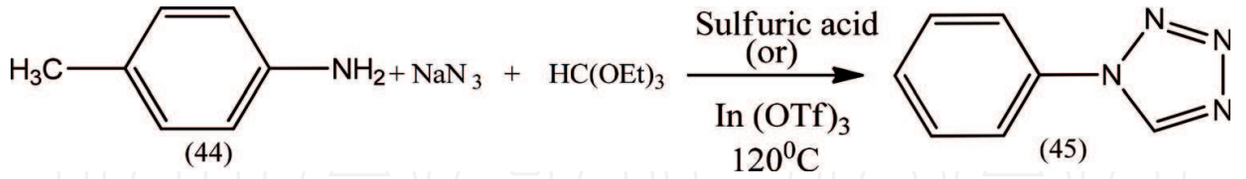


2.10. Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles catalyzed by methanesulfonic acid under neat conditions

A blend of chosen amine (**44**), triethyl orthoformate (0.4 ml), and sodium azide (0.13 g) was added to methanesulfonic acid (20 mol%). The blend was mixed for adjusted time, and the advance of the response was checked by TLC. The mixture was stirred for the specified time to obtain 1-substituted 1*H*-1,2,3,4-tetrazole (**45**) [46–50].

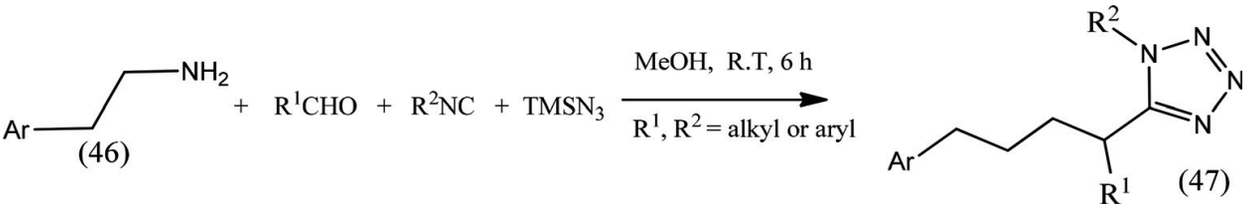


The above experiments yield very good result in the presence of various catalysts especially with silica sulfuric acid.



2.11. Productive synthesis of 1,5-disubstituted-1*H*-tetrazoles through an Ugi-azide procedure

The readiness of 1,5-disubstituted-1*H*-tetrazoles (**47**) was achieved in no catalyst conditions, optimized Ugi-azide process. The addition of aryl-ethanamine derivatives (**46**), aldehydes, isocyanides, and $TMSN_3$ in MeOH under mild conditions to give corresponding tetrazole (**47**) at room temperature [51–56].



2.12. Straightforward and proficient strategy for the synthesis of novel tetrazole derivatives and its antibacterial exercises

A progression of novel 5-phenyl-1-acyl-1,2,3,4-tetrazoles (**53**) has been combined by buildup of 5-phenyl-1,2,3,4-tetrazoles (**49, 51**) with different acylating reagents. The union of tetrazoles by the response of amines (**48, 50**) with sodium azide and triethyl orthoformate in acidic medium [34, 36, 57–59].

2.13. Synthesis and characterization of new 5-supplemented 1*H*-tetrazoles in water: a greener approach

A blend of carbonyl compound, malononitrile, and sodium azide in the presence of H_2O was mixed at 50°C for proper time to outfit the required tetrazole [34, 60–63].

*2.13.1. Synthesis of (1*H*-tetrazole-5-yl) acrylonitrile (NPTA)*

3-Nitro benzaldehyde (**54**) reacts with malononitrile in the presence of sodium azide to give NPTA (**55**).

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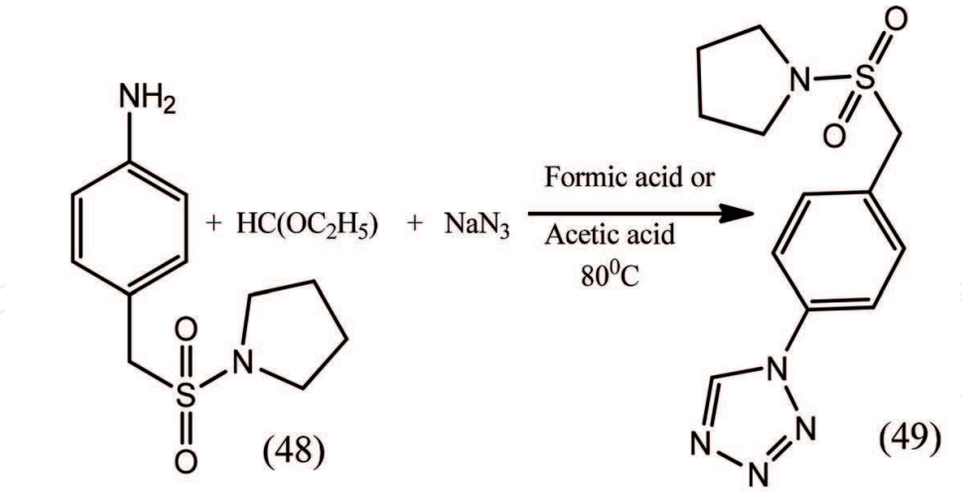
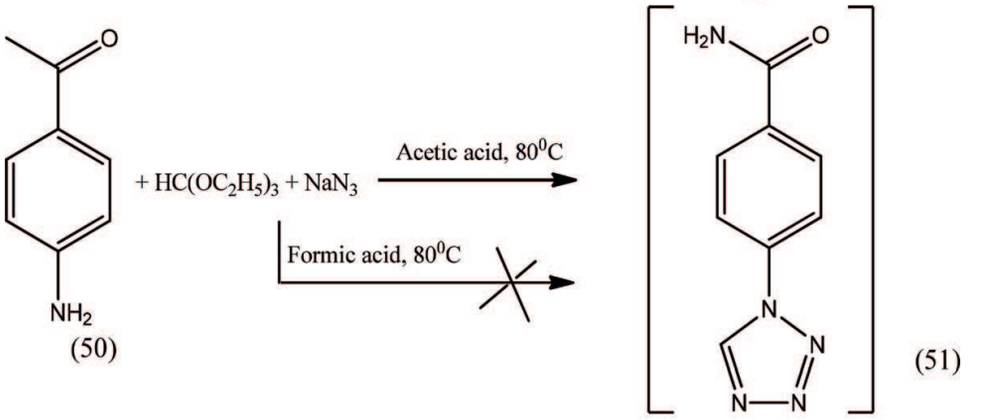
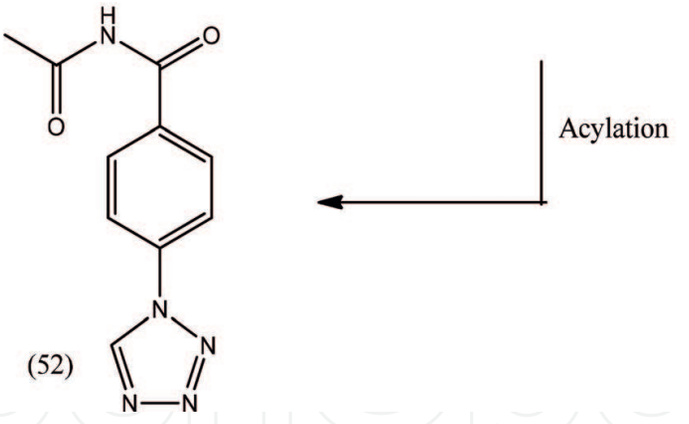
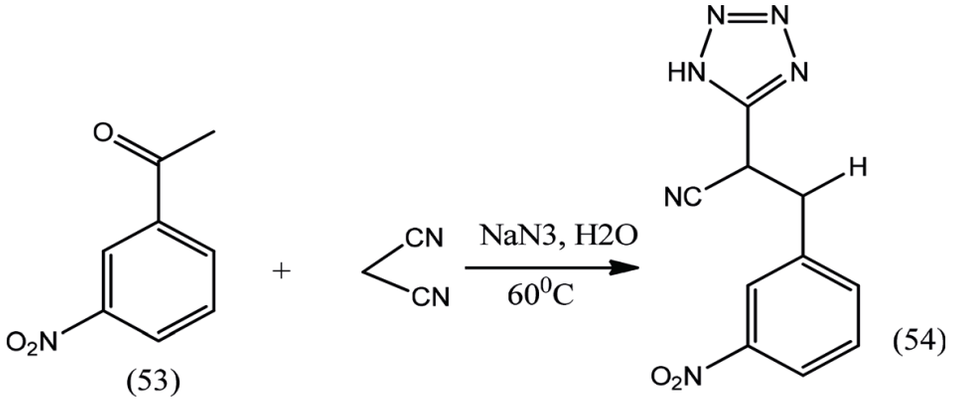


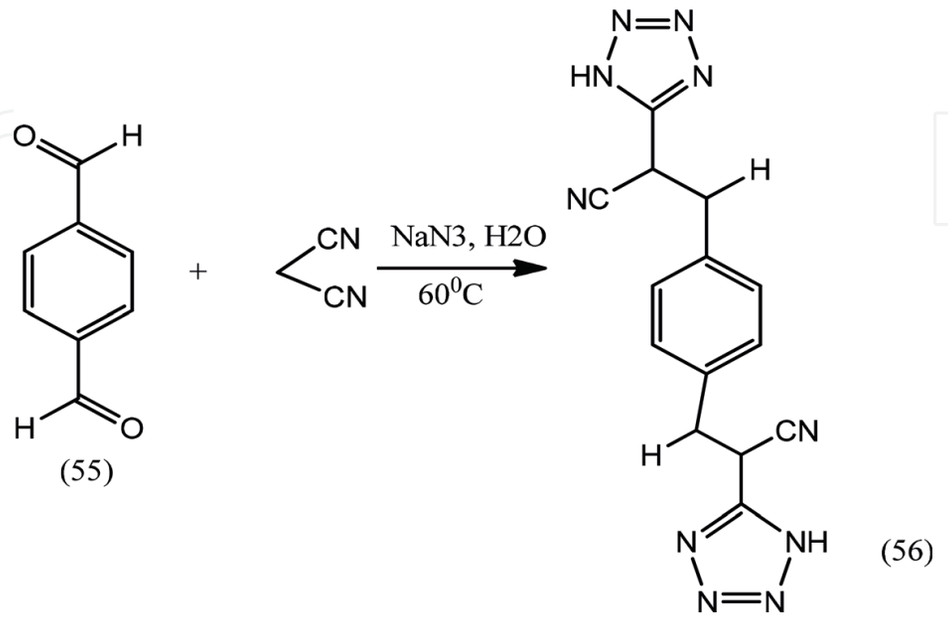






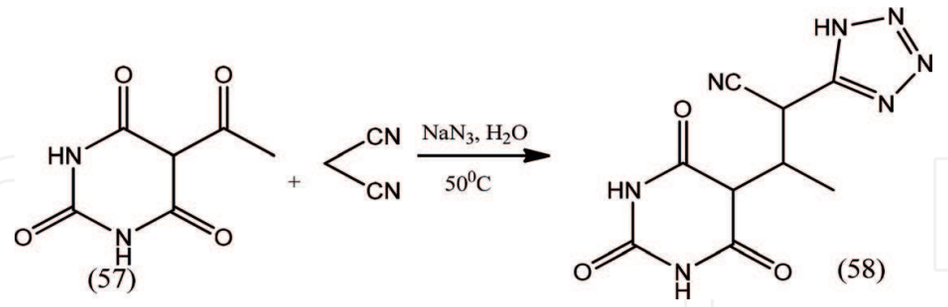
*2.13.2. Synthesis of (E)-3,3′-(phenyl)-bis (1,4(2-(1*H*-tetrazole-5-yl)) acrylonitrile) (PBTA)*

Aryl dicarbonyl compound (**55**) reacts with malononitrile in the presence of sodium azide to give PBTA (**56**).



*2.13.3. Synthesis of (z)-3-(hexahydro-2,4,6-trioxopyrimidine-5-yl)2-(1*H*-tetrazole-5-yl)-2-butane nitrile (BTBN)*

2,4,6-Trioxo derivative-5-yl compound (**57**) reacts with malononitrile in presence of sodium azide to give BTBN (**58**).



2.14. Preparation of 5-phenyltetrazole and its *N*-methyl derivatives

Azidation of benzonitrile (**59**) with dimethylammonium azide passive 5-phenyltetrazole dimethylammonium salt (**60**) was executed under microreactor setting. The energy of azidation of benzonitrile in DMF was examined at the range 80–95°C. The thermodynamic parameters of azidation under the microreactor conditions relate to the component of the 1,3-dipolar cycloaddition of azides to nitriles [17, 64–67].

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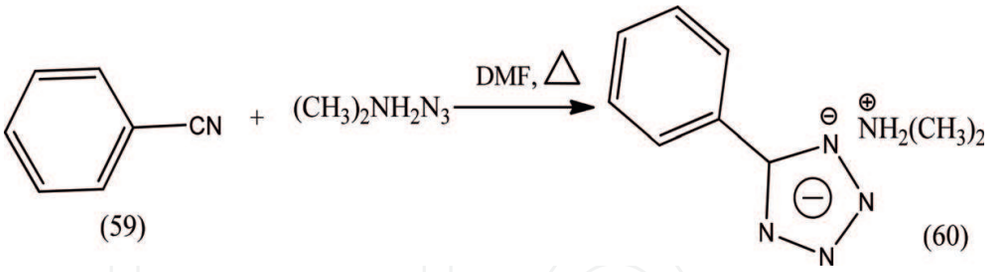
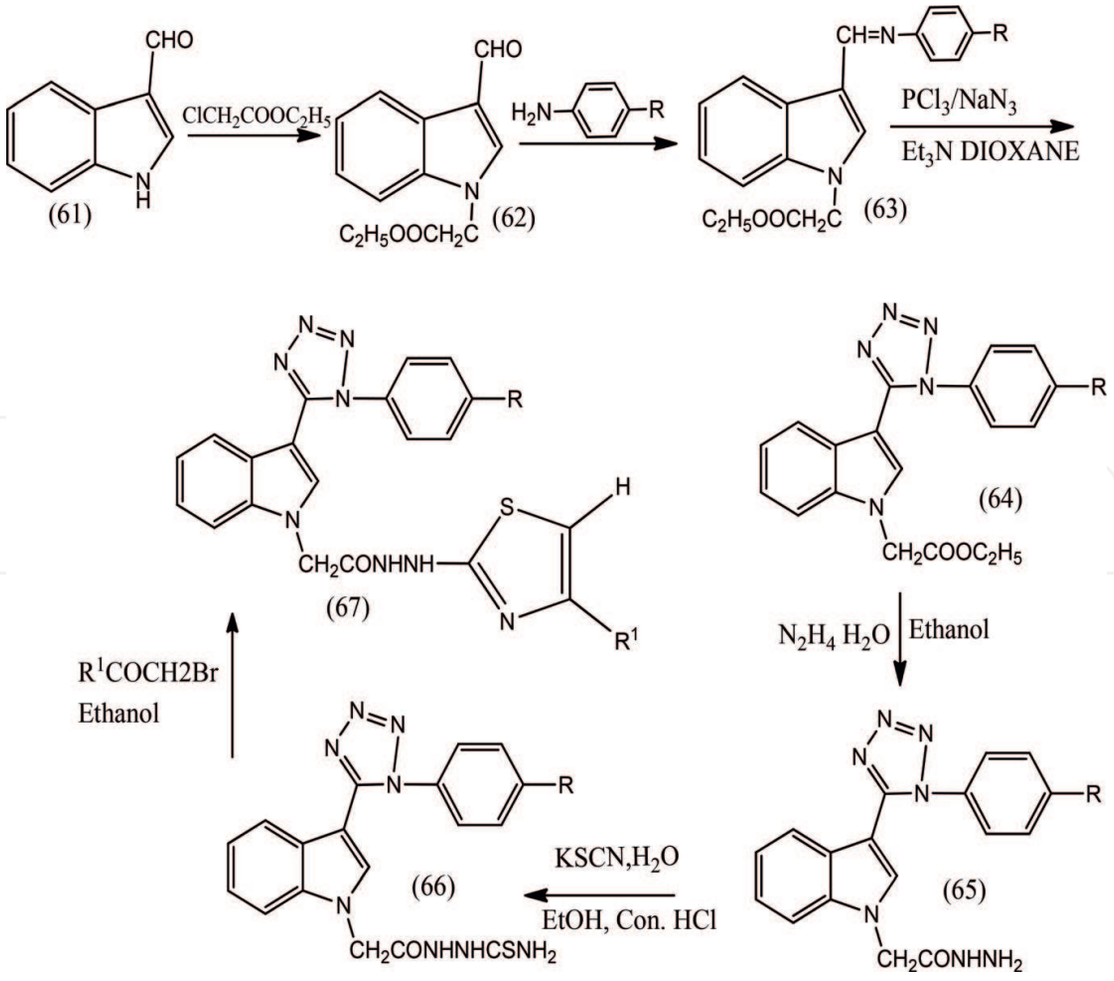


2.15. Synthesis, characterization, and biological examination of novel thiazole outcomes carrying indole moiety bearing tetrazole

A mixture of indole-3-carbaldehyde (**62**) and chloroethyl acetic acid was mixed in DMF. To this, anhydrous K_2CO_3 is included, and the response reaction mixture is mixed at room temperature (35°C) for 8 hours, to manage the effective yield of 2-(3-formyl-1*H*-indol-1-yl) acetate (**63**).



To this mixture, aniline, EtOH, and three drops of acidic corrosive are included and after that a warmed steam shower for 5–6 h to obtain the compound (**64**) ethyl 2-(3-phenyl amino)methyl-1*H*-indole-1-yl-acetic acid. Compound (**64**) is changed over into ethyl2-(3-(1-phenyl-1*H*-tetrazol-5-yl)-1*H*-indol-1-yl)acetate (**65**) by utilizing of conditions. Schiff base combination of thiazole subsidiaries containing indole moiety bearing tetrazole ring (**66**) was incorporated by the buildup of 2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1*H*-indole-1-yl) acetohydrazide with potassium thiocyanide and substituted ketones. At that point 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1*H*-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (**67**) is obtained [68–72].

2.16. A fast metal-free union of 5-substituted-1*H*-tetrazoles utilizing cuttlebone as a characteristic high compelling and minimal effort heterogeneous catalyst

Cuttlebone has a characteristic minimal effort heterogeneous impetus with high porosity. It carries high flexural firmness, high compressive quality, and high thermal solidness. Cuttlebone was taken out from cuttlefish (*Sepia esculenta*), which is ordinarily found in saltwater shorelines like Persian Gulf in Iran. This specimen can be found in a genuinely decent condition with negligible outer destruction. So as to evacuate contamination on the surface of cuttlebone, the catalyst has been powdered, washed with refined water, and dried at 100°C for 2 h [52, 73, 74]. The SEM image of cuttlebone was shown in **Figure 2**.

An advantageous, fast, and metal-free synthesis of 5-substituted-1*H*-tetrazoles (**70**) is depicted by [3+2] cycloaddition response of nitriles (**68**) with sodium azide (**69**).

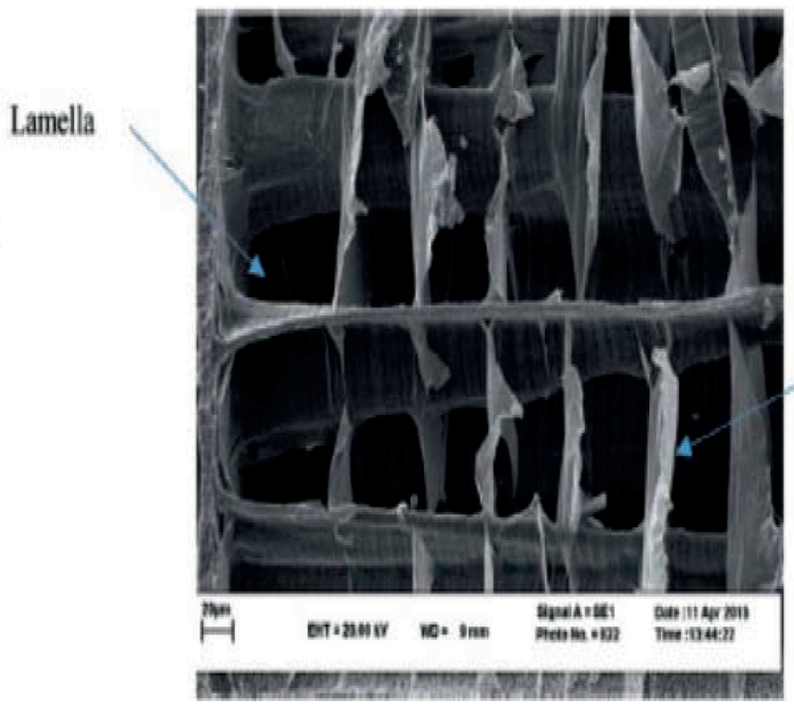


Figure 2. SEM image of cuttlebone.

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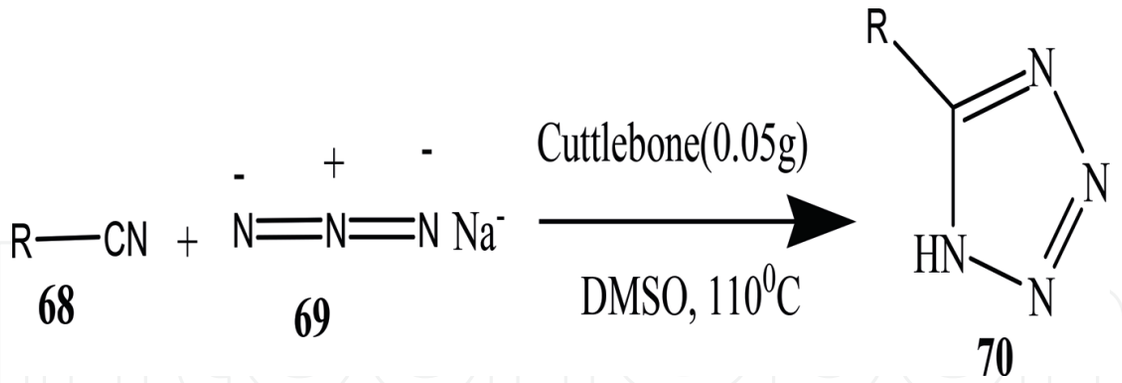

Figure 3 describes the system for the synthesis of 5-substituted-1*H*-tetrazoles within the sight of cuttlebone [30, 75].

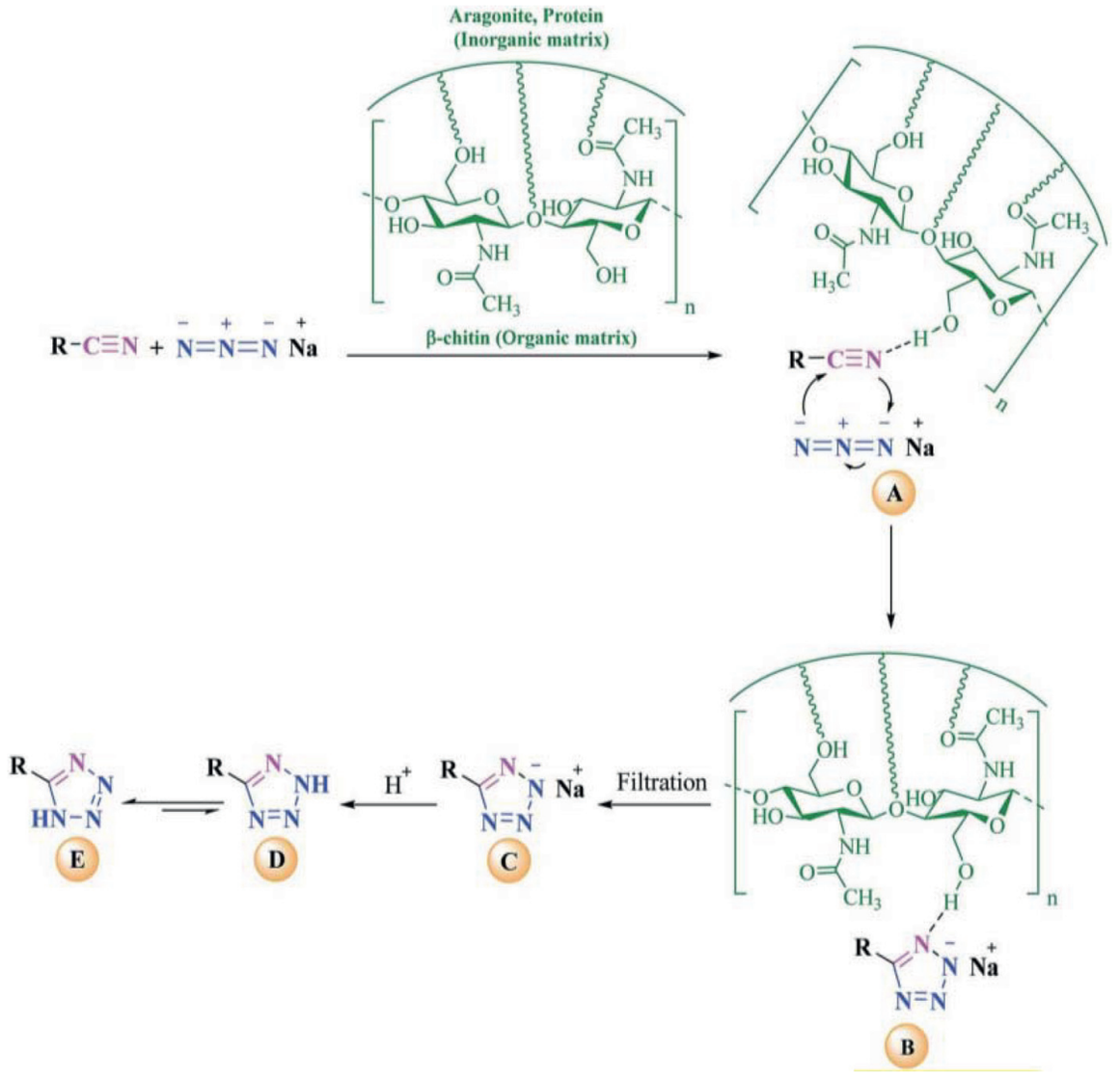

Figure 3. Synthesis of 5-substituted-1*H*-tetrazoles in the sight of cuttlebone.

3. Molecular docking-tetrazole derivatives

There are several literature reports pertaining to molecular docking studies of divergent tetrazole derivatives. We are citing a few for basic understanding of the readers who can explore this field a lot.

Very recently, Jonnalagadda et al. have synthesized some tetrazole-linked benzochromene derivatives and had their molecular docking study as well [76]. 5-Substituted 5-styryl terazolo [1,5-c]quinazoline derivatives were studied for their cytotoxicity and molecular docking by Parbhoo et al. [77]. In a similar fashion, several tetrazole derivatives were synthesized and subject to molecular docking in recent years [78–82].

4. Conclusion

The synthesis of tetrazole derivatives can be approached in various methods like ecofriendly, water solvent, moderate conditions, nontoxic, easy extractions, easy setup, low cost, etc. with good to excellent yields. The structural analysis was done by thermal and spectroscopic methods. Tetrazole and its derivatives play very important role in medicinal and pharmaceutical applications. Molecular docking studies play a vital role to decide the synthesis of pharmacologically relevant tetrazole derivatives in the near future. This facilitates, in fact, for new researchers to choose this topic as an apt and relevant research topic to explore.

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