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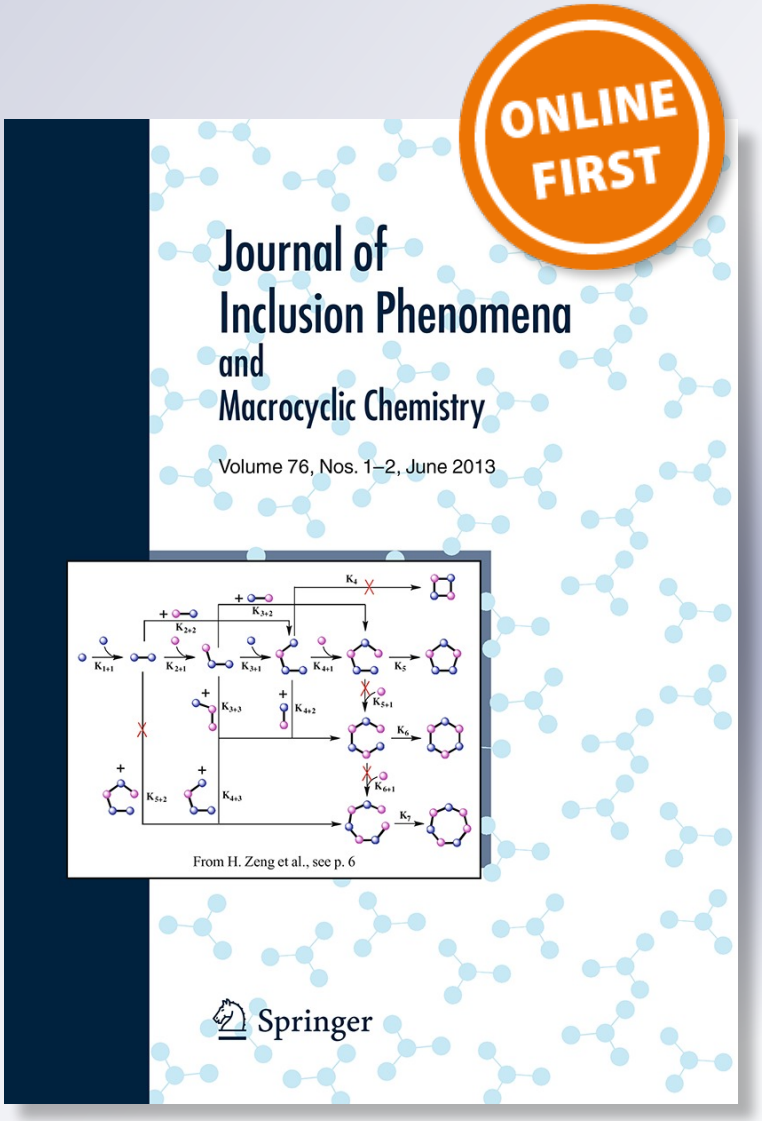

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REVIEW ARTICLE

Tetrazoles as carboxylic acid isosteres: chemistry and biology

Maqsood Ahmad Malik · Mohmmad Younus Wani · Shaeel Ahmed Al-Thabaiti · Rayees Ahmad Shiekh

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Abstract Tetrazoles are often used as metabolism-resistant isosteric replacements for carboxylic acids in SAR-driven medicinal chemistry analogue syntheses. Tetrazoles have not been found in nature; with rare exceptions, these compounds do not exhibit appreciable biological activity, but they are at the same time resistant to biological degradation. This property makes it possible to use tetrazoles as isosteric substituents of various functional groups in the development of biologically active substances. The tetrazole motif has been used in various drug pharmacophores as a suitable replacement of carboxylic acid moiety and different methods have been used for the synthesis of tetrazoles using different reaction conditions. This review tries to give a vivid look on the different synthetic methods, using catalysts or different reagents for the synthesis of tetrazoles. The biological importance of tetrazoles has also been highlighted.

Keywords Tetrazole · Bioisosterism · Synthesis · Biological properties

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Introduction

The quantity and the interest of research devoted to the synthetic methods, molecular structure, physicochemical properties and application of tetrazoles constantly increases [1–5]. This heteroaromatic system contains the maximum number of nitrogen atoms, which is the reason why tetrazoles exhibit the extreme values of acidity, basicity, and complex formation constants. They have specific thermochemical properties and exhibit multiple reactivity [6–8]. The tetrazole ring is the fragment of a number of modern drugs (antibacterial, anti-allergic, anti-inflammatory, angiotensine II antagonists, etc.). Because of tetrazoles being highly effective explosives, rocket fuel and gas generating compositions have been developed [9–12]. Because of the various possibilities of coordination of tetrazole ring with metal ions, these compounds can be used as effective complexones and corrosion inhibitors [13–16]. The presence of several reaction centers and the possibility of prototropy in tetrazoles afford the conditions for their use in organic and bioorganic synthesis as reagents and catalysts [17, 18]. Many of the above-mentioned properties of NH-unsubstituted tetrazoles are related to their ability to act as acids and bases, and also to the possibility of prototropic annular tautomerism in the case of neutral molecules and conjugated acids [19, 20] Tetrazoles exhibit potential biological activity because the tetrazole ring is considered a biomimic of the carboxylic acid functional group (Fig. 1). However, the tetrazole moiety is metabolically more stable than the carboxylic acid group. Concerning the synthetic methodologies developed for the preparation of tetrazoles, the main ones are based on cyclization reactions involving Sodium azide- the most efficient method used to produce tetrazoles involves the use of sodium azide. There are many ways to prepare tetrazoles

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from different starting materials. Most of these methods involve the use of azides. Their preparation from nitriles commonly involves the use of an amine hydrochloride and sodium azide. A number of different 5-substituted tetrazoles have been prepared from nitriles using sodium azide and an excess of triethylamine hydrochloride in aromatic solvents [21–23]. Another method has been reported where nitriles react with sodium azide and a stoichiometric amount of acetic acid in tert-butyl alcohol [24]. Extreme care must be taken with these types of reactions to monitor any possible HN_3 in the headspace of the reactor to avoid explosive levels of hydrazoic acid. Other different methods can be adopted for the preparation of tetrazoles from nitriles where dangerous levels of hydrazoic acid can be avoided. The use of trialkyltin azide [25] or trialkylsilylazide in conjunction with either dialkyltin oxide [26] or trimethylaluminum [27] has been reported but each suffers from a difficult initial reagent synthesis. These systems using tin lead to problematic separations of tin from the product and involve careful handling of toxic tin. Systems containing trimethylaluminum include laborious catalyst neutralization and waste disposal as well as careful handling due to moisture sensitivity. A method using tetramethylguanidinium azide [28] has been reported but suffers from dangerous reagent synthesis involving the direct use of HN_3. The use of a surfactant in conjunction with ammonium chloride and sodium azide [29] has been developed but is limited due to long reaction times in excess of 5 days. Keeping in view the stability of tetrazoles, their usefulness in synthetic organic chemistry, biology and other fields, more studies should be continued for the elucidation of the chemistry and biology of these compounds. Over 300 members of this class of nitrogen heterocyclic have been prepared and have been extensively investigated. There has been no recent comprehensive review on tetrazoles particularly of their chemistry and biology. Importantly we have also made some investigations of this moiety and tried to reveal its biological properties. This review will try to give a vivid look on the various synthetic routes applied and the biological properties of these compounds.

Tetrazoles as bioisosteres

Bioisosteres are substituents or groups that impart similar biological properties to a chemical compound; for example, the bioisosteric replacement of a hydrogen atom with a fluorine atom within a drug molecule will generally have no influence on the drug's efficacy, but it may prolong the drug's half-life by inhibiting metabolic oxidation. Thus, the purpose of exchanging one bioisostere for another is to fine tune the pharmacokinetic or pharmacodynamic properties of a bioactive compound. Although the chemical and physical basis of equivalence for most classical bioisoteric substitutions is obvious (e.g., hydrogen to fluorine, ester to amide, phenyl to thiophene), there are number of nonclassical bioisosteric substitutions for which the physicochemical similarities between the two bioisosteres are not readily apparent. Although the chemical and physical basis of equivalence for most classical bioisoteric substitutions is obvious (e.g., hydrogen to fluorine, ester to amide, phenyl to thiophene), there are a number of nonclassical bioisosteric substitutions for which the physicochemical similarities between the two bioisosteres are not readily apparent.

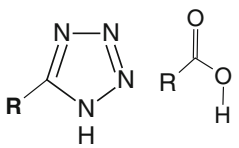


Fig. 1 Structural comparison of carboxylic acid moiety and tetrazole ring

The coining of the term bioisosterism goes back to the pioneer work of Friedman and Thornber during the early 50 s. Friedman, [30] recognizing the usefulness of the concept isosterism to design bioactive molecules, defined bioisosters as compounds which fit the definitions of isosteres and which exercise their biological activity of bioreceptor, whether through agonist or antagonist actions. However, Friedman introduced the term bioisosterism to describe the phenomenon observed between substances structurally related which presented similar or antagonistic biological properties [30]. Later, Thornber [31] proposed a broadening of the term bioisosteres, defining them as subunits or groups or molecules, which possess physicochemical properties of similar biological effects. It is a major challenge to convert a compound binding with high affinity to a biological target (i.e. a hit, lead or candidate molecule) into a successful drug on the market. A lead compound with desired pharmacological activity may have undesirable characteristics that limit its bioavailability or structural features, which adversely influence its metabolism and excretion from the body. It may also possess unwanted side effects or toxicity. Bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. A bioisostere can be considered as a compound resulting from the exchange of an atom or groups of atoms with another, broadly similar, atom or groups of atoms. The objective of a bioisosteric replacement is thus to create a new compound with similar biological properties to the parent compound.

Tetrazoles have received a particular interest of the medicinal chemist because they probably constitute the most commonly used bioisostere of the carboxylate moiety [32] (Fig. 2). Tetrazoles are ionized at physiological pH and exhibit a planar structure like their carboxylic acid

counterparts. However, Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylates while having similar acidity (p*K*a 4.5–4.9 vs. 4.2–4.4 respectively) [33]. The increase in lipophilicity could account for the higher membrane permeability seen with tetrazole bioisosteres. In a series of PTB1B inhibitors Liljebris et al. [34] reported that the introduction of a more lipophilic tetrazole resulted in significantly higher Caco-2 cell permeability than the corresponding carboxylate analogue (Fig. 2).

Substituted 5-aryl tetrazoles are stronger acids than the comparable benzoic acids due to enhanced resonance stabilisation of the aryl tetrazolate anion compared to the carboxylate anion. The electron withdrawing groups at the para-position of the 5-phenyl ring increases the acidity of the 5-phenyltetrazolic acids and para-electron donating substituent have the reverse effect and is in agreement with substituent effects in benzoic acids. However, the well known acid strengthening effect of ortho-substituents does not apply in the 5-aryltetrazolic acid series. Changes in annular conjugation effects arising from loss of ring coplanarity are likely to contribute to these differences. It should be pointed out that 5-substituted tetrazoles that contain a free N–H bond exist as a nearly 1:1 ratio of 1*H* and 2*H*-tautomeric forms (Fig. 3).

A major advantage of tetrazoles over carboxylic acids is that they are resistant to many biological metabolic degradation pathways. Tetrazoles escape most of the Phase II bio- transformation of carboxylic acids. Benzoic acid substrates often undergo covalent bond formation with transferase enzymes to form activated species which then undergo conjugation transformations by a variety of pathways. The analogous reaction activation process does not occur with aromatic or aliphatic tetrazoles. However, tetrazolic acids have been shown to form β-glucuronides, a metabolic fate that often befalls aliphatic carboxylic acids, and both tetrazole tautomers may serve as substrates for *N*-glucuronidation. The long half life seen with a number of orally administered tetrazole acid containing compounds has been attributed to enterohepatic recirculation mechanisms [35]. While *N*-glucuronide formation and subsequent biliary excretion of a tetrazole acid may remove the drug from circulation, reabsorption of the metabolite may result in hydrolysis in the intestinal mucosa, thereby allowing additional assimilation of the parent drug in a second pass.

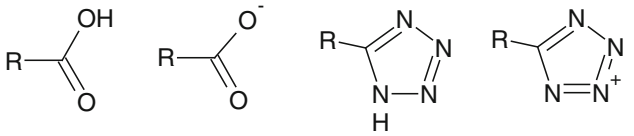


Fig. 2 Structural relations between 5-substituted tetrazoles and carboxylic acids

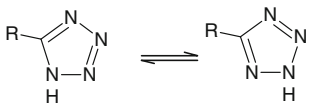


Fig. 3 The two possible tautomers of 5-substituted tetrazoles

A retained pharmacological effect and a more favourable pharmacokinetic profile are often achieved by the replacement of a carboxylate with a metabolically stable tetrazolate. Notable examples of tetrazoles as carboxylate bioisosteres include: protein tyrosine phosphatase 1B (PTB1B) inhibitors, [34] metabotropic glutamate (mGlu1) receptor agonists, [36] growth hormone secretagogues, [37] and cysteinyl leukotriene D4 (LTD4) receptor agonists [38].

Matta and his co-workers have used computational method and evidence to explore the utility of the electron density and the electrostatic potential as the basis for a systematic investigation of the physical and chemical similarities between bioisosteres [39]. They used tetrazole (5-methyl tetrazole) and carboxylate (ethanoic acid) bioisosteric pair as an illustrative example for this study (Fig. 4). These model compounds contain either a tetrazole or carboxylate functional groups capped with a methyl group. It is observed that tetrazole and carboxylate anions give rise to electrostatic potentials (ESP) that show a significant local similarity in the disposition of four coplanar local minima at positions consistent with lone pairs [39]. It has been provided computational evidence that the bioisosteric similarity of tetrazole and carboxylate anions arises from a similarity in the geometrical arrangement of four local minima in their respective electrostatic potentials (a quartet of minima). It has been observed by Matta et al. [39] that the geometrical arrangement is not significantly distorted when the capping group to which the bioisosteres are attached is changed.

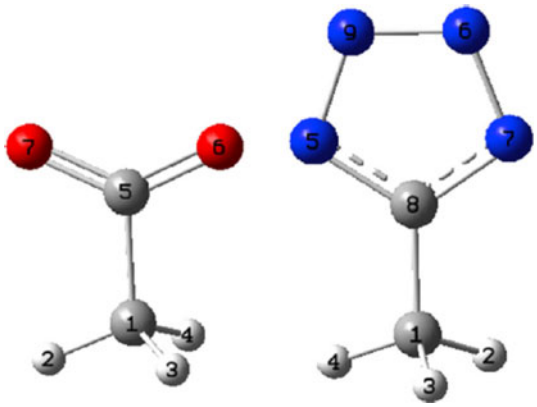


Fig. 4 A ball-and-stick representation of the optimized geometries of acetate (*left*) and of 5-methyl tetrazole (*right*)

Synthesis of tetrazoles by different methods

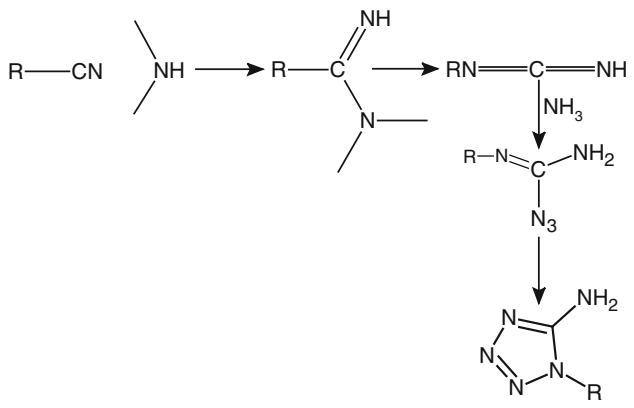
Synthesis of tetrazole derivatives is obviously an important task in modern medicinal chemistry. Although a number of synthetic methods are available, there still exists a demand for improved protocol which allows an effective transformation in the presence of a wide range of functional groups. The chemistry of heterocycles has acquired immense importance in recent years. The tetrazole function is metabolically stable and a close similarity between the acidic character of the tetrazole group and carboxylic acid group have inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents.

Hantzsch and Vagt [40] who prepared 5-amino tetrazole by the interaction of hydrazoic acid and cyanamide, first observed the addition of hydrazoic acid to the cyanide group with the formation of 5-substituted tetrazole derivatives. Some 20 years later Stolle [41] showed that the same product could be prepared from the more readily accessible dicyandiamide and hydrazoic acid. Other methods of preparing 5-substituted tetrazoles have been reviewed [42]. In 1932 Braun and Keller [43] reported attempts to bring about reaction of hydrazoic acid with a number of alkyl and aryl cyanides in the presence of concentrated sulfuric acid. Under these conditions a reaction between 2 mol of hydrazoic acid and one of the nitrile took place and the formation of 1-alkyl or aryl-5-aminotetrazole derivatives indicated that a rearrangement of the nitrile with a shift of the alkyl group from carbon to nitrogen had taken place during the reaction. They suggested that the reaction involved the addition of an imine radical (HN=C) to the cyanide group to form an intermediate which after rearrangement added a molecule of hydrazoic acid and cyclized to form the 5-aminotetrazole derivative (Scheme 1).

Braun and Keller [43] concluded that hydrazoic acid would not add to the cyanide group of the nitriles of carboxylic acids. Repetition of Dimroth's preparation of tetrazole in benzene solution rather than in alcoholic solution as originally suggested has made it possible to develop this procedure into a useful preparative method. Furthermore, a study of the interaction of hydrazoic acid with dicyandiamide in aqueous solution showed this reaction to take place with such remarkable ease that it could be used for the preparation of 5-aninotetrazole in excellent yield in almost any desired quantity. These observations suggested the desirability of studying again the interaction of alkyl and aryl cyanides with hydrazoic acid in the absence of reagents such as sulfuric acid. This was particularly desirable in view of the work of Newman and Gildenhorn [44] and Smith [45], which had demonstrated the readiness with which rearrangement of addition products of hydrazoic acid, and unsaturated groupings took place in the presence of proton donors. The formation of 5-substituted tetrazoles by interaction of hydrazoic acid and nitriles may be explained most easily by the assumption of an intermediate imide azide which rapidly cyclizes to form the tetrazole as suggested by Dimroth and Fester [39] Although it is unlikely that the imide azide would be stable at the elevated temperature employed, the formation of such an intermediate seems reasonable since Vommina et al. [46] reported synthesis of *N*-Fmoc amino acid derived 1-substiututed tetrazoles (3) from isonitriles (2) refluxed with trimethylsilyl azide in presence of $ZnBr_2$ as a catalyst in dry MeOH solvent for about 6 h. (Scheme 2). This class of tetrazoles is accessed by the dipolar cycloaddition of azide with isonitriles.

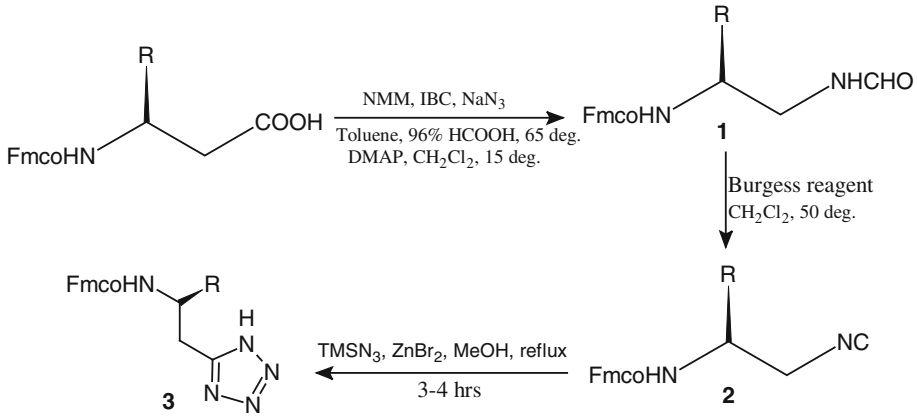
Mansoori et al. [47] reported synthesis of new bis(5-oxy-1*H*-tetrazole) derivatives (Scheme 3). Different bisphenols reacted with cyanogen bromide in the presence of triethylamine as base in acetone at 0–5 °C to give the corresponding bis-cyanates. Treatment of the latter with sodium azide afforded (after acidification) the desired bis-tetrazoles. It is a convenient method for synthesis of bis-tetrazoles.

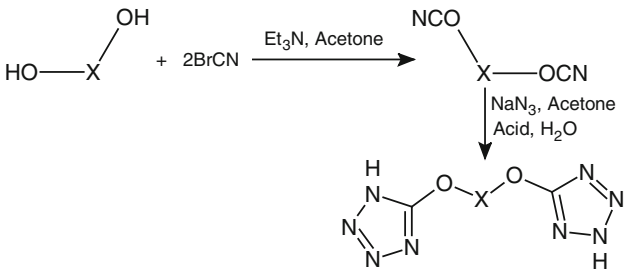
Sharpless and co-workers [48, 49] reported synthesis of tetrazoles by refluxing the starting material in water/2-propanol at 80 °C with sodium azide and catalytic zinc bromide (Scheme 4). The most convenient route to 5-substituted 1*H*-tetrazoles is the addition of azide ion to nitrile [50]. Jiun-Jie et al. [51] also reported direct transformation of primary alcohols and aldehydes into tetrazoles in aqueous media (Scheme 5). The alcohols and aldehydes reacted with iodine in ammonia water to provide the corresponding nitrile intermediates which readily underwent [2 + 3] cycloadditions with sodium azide on exposure to microwave irradiation to give the corresponding triazines and tetrazoles. This method is largely used because ease in workup and high yields. Shie and Fang [52] in yet another study have found a direct method for transformation of



Scheme 1 Schematic representation of formation of 5-amino tetrazole

Scheme 2 *N*-Fmoc amino acid derived 1-substiututed tetrazoles by using isonitriles

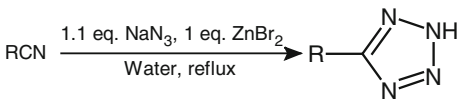




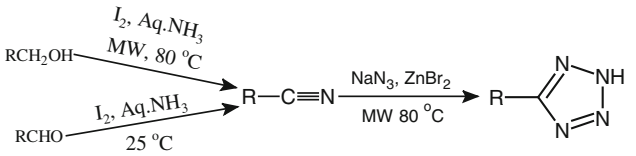
Scheme 3 Synthesis of new bis (5-oxy-1*H*-tetrazole) derivatives by using bis-cyanates

aldehydes to nitriles by using iodine in ammonia water instead of liquid ammonia or ammonia gas saturated in alcohol solvents. The corresponding nitriles are then cyclized into tetrazoles using NaN_3 and $ZnBr_2$. This transformation is completed within a short period (<1 h) at room temperature. A variety of aldehydes, including aromatic, heterocyclic, aliphatic, conjugated and polyhydroxy aldehydes, have thus been converted to their corresponding nitriles in high yields (83–97 %). This transformation utilizes iodine as an appropriate oxidant and presumably proceeds with an intermediate of N-iodo aldimine (Fig. 5) which eliminates an HI molecule in ammonia solution to afford the nitrile product. This type of tandem reaction in a one-pot procedure provides an expedient route to amides, triazoles and tetrazines besides tetrazoles.

Synthesis of α-amino tetrazoles have also been reported by Demko and Sharpless [48] by simple heating of the N-protected α-amino nitrile in a water/2-propanol mixture at reflux (80 °C) in the presence of sodium azide and zinc bromide (Scheme 6). Not only are these solvents environmentally benign, they also facilitate isolation, since



Scheme 4 Sharpless et al., method



Scheme 5 Direct conversion of alcohols and aldehydes to tetrazoles

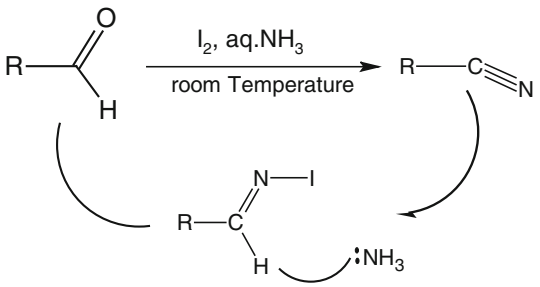
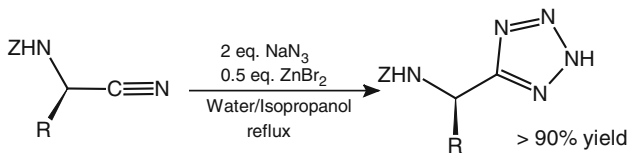


Fig. 5 Proposed mechanism of nitrile formation via intermediate of N-iodo aldimine

acidification and extraction are usually sufficient to provide the product as a pure solid. In cases where the α-amino nitrile is protected as the benzyl carbamate and not unusually hindered, yields are at or above 90 %. The reaction conditions have little effect on the enantiomeric purity of α-amino nitriles with aliphatic side chains and the corresponding tetrazole is obtained with yields above 85 %. In another study the same group of workers have reported the synthesis of tetrazoles from nitriles in water using NaN_3 and $ZnBr_2$. The authors have proposed a mechanism of this reaction based on kinetic studies using a water-soluble nitrile [49]. The study revealed first-order dependence in both nitrile and azide and one-half order dependence for zinc bromide. The mechanism of the addition of hydrazoic acid/azide ion to a nitrile to give a tetrazole has been debated, with evidence supporting both a two-step mechanism and a concerted [2 + 3] cycloaddition (Fig. 6). These mechanistic studies implied that the role of zinc is not simply that of a Lewis acid; a number of other

Lewis acids have been tested which caused little to no acceleration of the reaction. In contrast, Zn^{2+} exhibited tenfold rate acceleration at 0.03 M, which corresponds to a rate acceleration of approximately 300 at the concentrations typically used. The exact role of zinc is not yet clear.

In yet another study towards the intramolecular [2 + 3] cycloaddition of organic azides with heteroaromatic nitriles Demko and Sharpless [53] have surprisingly found that nitriles attached to heteroatoms are also highly competent partners for intramolecular cycloaddition reactions with organic azides. Cyanates, thiocyanates, and cyanamides are all competent dipolarophiles for this reaction. This report describes the first examples of the synthesis of 1,5-fused tetrazoles via an intramolecular [2 + 3] cycloaddition wherein the pendant nitrile component is attached to a heteroatom O, S, N (Scheme 7). The most common route towards these fused tetrazolo ring systems is via the imidoyl azide, which spontaneously cyclizes to the tetrazole. Imidoyl azides are typically formed by nucleophilic attack of azide anion on an imidoyl chloride, [54] a related species [55] (Scheme 8), or by nitrosation of an imidoyl hydrazine [56]. A less common route begins with the 5-heterosubstituted 1*H*-tetrazole from which the fused bicyclic ring system is subsequently formed [57]. The range of the azidonitrile species which participate in these intramolecular [2 + 3] cycloadditions is quite broad. The tetrazoles formed can be fused to five- or six-membered ring systems which can be either saturated or unsaturated, and the heteroatom (Scheme 7), can be nitrogen, oxygen, or sulfur. The [2 + 3] reaction itself is highly reliable; therefore, where the reported yields are moderate, product decomposition is the suspected cause. Also noteworthy is the better synthetic access to the precursors than for the analogues with all-carbon tethers -two-carbon -carbon σ-bonds are replaced by two carbon-heteroatom σ-bonds, with the latter generally being easier to make [58]. Simple heating of the azido cyanamides in solution at 130–140 °C usually provides pure tetrazole. Azido-*N*,*N*-disubstituted cyanamides (R_2NCN) of various geometries are excellent substrates. However, their N–H analogues yield predominantly side products, involving the "apparent" displacement of cyanamide (Scheme 9). Strain introduced by trans-ring fusion between the scaffold and the enclosed ring can affect reaction times and yields.



Scheme 6 Synthesis of α-aminotetrazole from an α-aminonitrile in water via zinc catalysed addition of azide

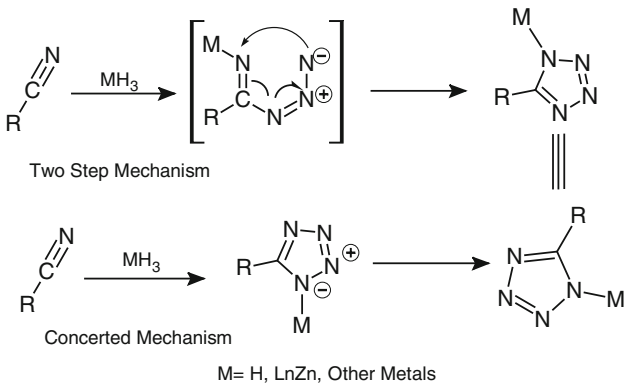
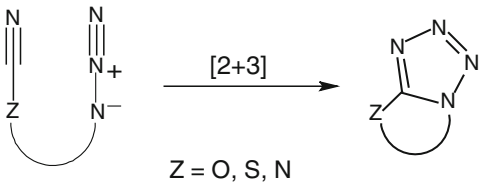
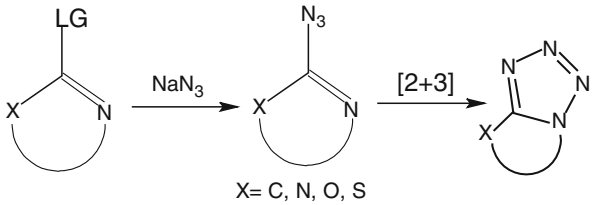


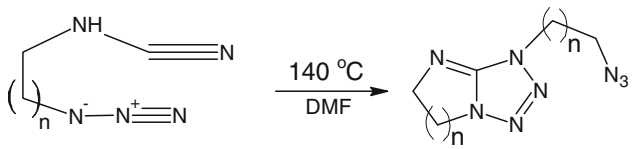
Fig. 6 Mechanism of tetrazole formation



Scheme 7 [2 + 3] cycloaddition of heteroatom bound nitriles to tetrazoles

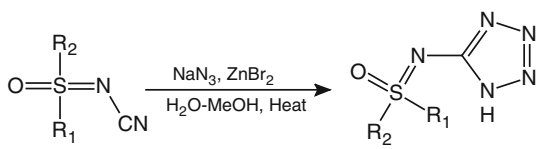


Scheme 8 Synthesis of fused tetrazoles via imidoyl azide



Scheme 9 Synthesis of tetrazoles using azido cyanamides

Mancheno et al. [59] synthesized *N*-(1*H*)-tetrazole sulfoximines type of derivatives (Scheme 10). *N*-(1H)-Tetrazole sulfoximines are readily available by addition of sodium azide to the corresponding *N*-cyano derivatives in the presence of $ZnBr_2$ used as catalyst. The *N*-(1H)-



Scheme 10 Synthesis of *N*-(1*H*)-tetrazole sulfoximines

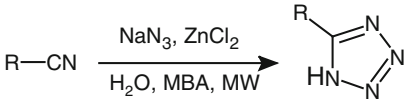
tetrazoles are used as intermediates in the synthesis of other *N*-heterocyclic sulfoximines.

Myznikov et al. [60] synthesized 5-substituted tetrazoles by cycloaddition of nitriles of diverse structures with sodium azide in presence $ZnCl_2$ under the microwave irradiation to give in good yields 5-substituted tetrazoles (Scheme 11). Finnegan et al. [61] have also synthesized 5-substituted tetrazoles in high yields by heating nitriles of diverse structure with sodium azide in DMF in the presence of ammonium chloride (Scheme 12). Afterwards the Finnegan method obtained universal recognition and was widely applied to the preparation of versatile 5-substituted tetrazoles.

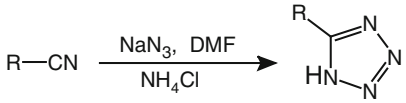
Mohite et al. [62] have reported a series of novel 5-phenyl, 1-acyl 1,2,3,4-tetrazoles (2–5) synthesized via condensation of 5-phenyl-1,2,3,4-tetrazoles with various acylating reagents (Scheme 13). Weifa et al. [63] synthesized 2-trifluoromethyl-1-[(2-1*H*-tetrazole-5-yl-biphenyl -4-yl) by reaction of 2-trifluoromethyl-1-[(2-cyanobiphenyl -4-yl) methyl] benz- imidazole with sodium azide and $Et_3N{\cdot}HCl$ used as catalyst in 1-methyl-2- pyrrolidinone (Scheme 14).

Alam et al. [64] report a simple and efficient method for the preparation of 5-arylamino-1*H* (2*H*)-tetrazoles and 5-amino-1-ary-1*H*-tetrazoles with excellent yields and high purity from secondary arylcyanamides at room temperature in glacial acetic acid (Scheme 15). Biot et al. [65] reported the synthesis of tetrazole derivatives of naphthoquinone carboxylic acid which is a potent *Plasmodium falciparum* GR inhibitor. By treating cyanoethyl amide with sodium azide and triflic anhydride use as catalyst in CH_3CN obtained in high yields and purity (Scheme 16).

Hajra et al. [66] developed a versatile and highly efficient protocol for the synthesis of 1,5-disubstituted tetrazoles by a metal triflate catalyzed one-pot reaction of alkenes, NBS, nitriles, and $TMSN_3$ (Scheme 17). Among the metal triflates, $Zn(OTf)_2$ was found to be the best catalyst. Use of different combinations of alkenes and nitriles generated a variety of 1,5-disubstituted tetrazoles containing an additional R-bromo functionality of the N1-alkyl substituent. Jacobson and Amstutz [67] report new methods for the synthesis of 1,5-disubstituted tetrazoles containing the carboxyl group as the functional component (Scheme 18). Another new type of tetrazole derivative containing the carboxyl group has been prepared by



Scheme 11 Synthesized 5-substituted tetrazoles by cycloaddition of nitriles with sodium azide in presence of $ZnCl_2$ under the microwave irradiation



Scheme 12 Synthesis of 5-substituted tetrazoles in DMF in the presence of ammonium chloride

condensing 1-phenyl-5-methyltetrazole and 1-methyl-5-benzyltetrazole with diethyl oxalate in refluxing ethanol solutions of sodium ethoxide producing ethyl 1-phenyl-5-tetrazolylpyruvate and ethyl P-phenyl- methyld-tetrazolyl-pyruvate.

Ronald and Vilmars [68] have synthesized 5-Methyl-tetrazole derivatives from the corresponding nitriles by standard synthetic methods (Scheme 19). Wang and Lin [69] efficiently synthesized six photoreactive tetrazole amino acids using the de novo Kakehi tetrazole synthesis method by reaction of protected 4-formyl phenylalanine, $PhSO_2NHNH_2$ and phenyldiazonium chloride in excellent yield (Scheme 20). Yathirajan and co-workers [70] reported synthesis of 5-(4′-methyl-1,1′-biphenyl-2-yl)-1H-tetrazole (MBT) from cyclo addition of 4′-methyl-1,1′-biphenyl-2-corbonitril (**1**) with trimethyl tin azide (Scheme 21).

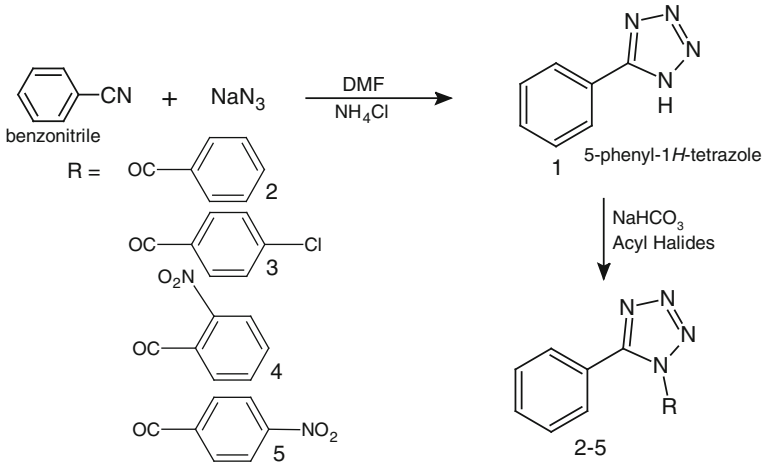
Lim et al. [71] reported synthesis of 5-dinitromethyl-tetrazole (Scheme 22) from ethyl-5-tetrazolyldinitroacetate using water. Formation of 5-dinitromethyltetrazole has also been accounted in various literatures [72]. Harel and Rozen [73] developed an efficient procedure for synthesis of 1,5-disubstituted tetrazole 3-N-oxide derivatives from 1,5-disubstituted tetrazole using using $HOF{\cdot}CH_3CN$ (Scheme 23).

Mehta et al. [74] reported synthesis of *N*-pentanoyl-*N*-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl] methyl}-L-valine (4) from inexpensive and commercially available valeryl chloride and L-valine methylester hydrochloride via Negishi coupling from aryl bromide (1) and 5-phenyl -1-trityl-1*H*-tetrazole (2) (Scheme 24).

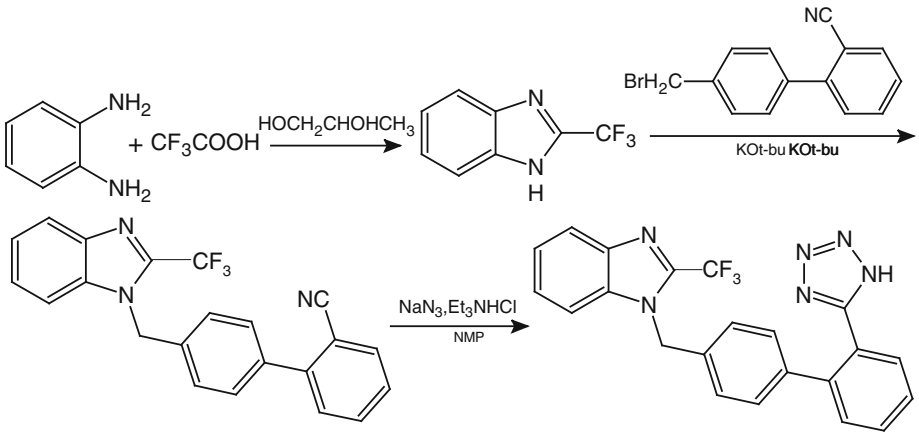
Santos and co workers [75] have synthesized 5-(4-hydroxyphenyl)-2-*n*-alkyltetrazoles by cycloaddition of nitriles with sodium azide in DMF (Scheme 25). Voitekhovich et al. [76] obtained hitherto unknown 2-(1-methylvinyl) tetrazoles by regioselective alkylation of tetrazole and 5R-tetrazoles with 1-halogenopropan-2-ols and 3-bromopropene followed by dehydrohalogenation of the intermediate products in high yield (Scheme 26).

Su et al. [77] synthesized a series of 1-substituted 1*H*-1,2,3,4-tetrazole compounds in good yields from amines, triethyl orthoformate, and sodium azide through the catalyzed reaction with $Yb(OTf)_3$ (Scheme 27). Hanessian et al. [78] reported synthesis of oxabicyclic tetrazoles from 2,2α-substituted 1,3-dioxolanes and from azido ethyl esters treatment with TMSCN and BF_3OEt_2 lead to a

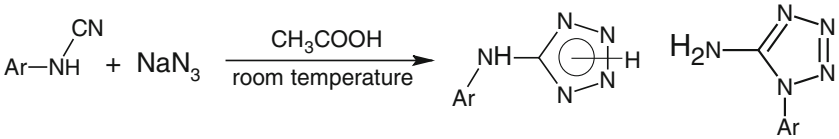
Scheme 13 Synthesis of novel 5-phenyl,1-acyl 1,2,3,4-tetrazoles



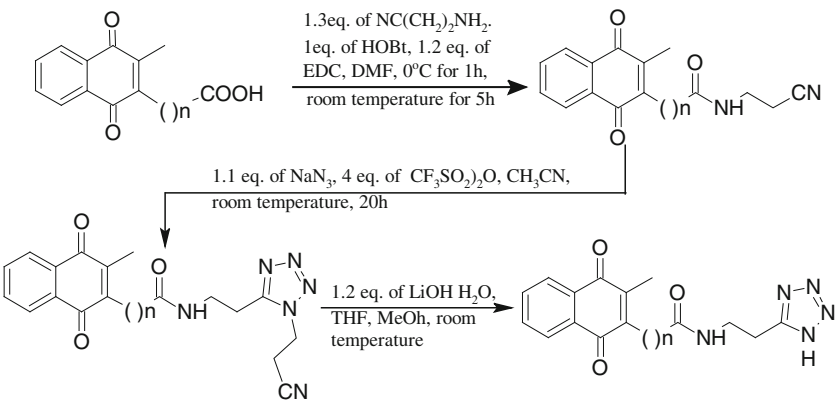
Scheme 14 Preparation of 2-trifluoromethyl-1-[(2-1H-tetrazole-5-yl-biphenyl-4-yl) methyl] benzimdazole



Scheme 15 Synthesis of 5-arylamino-1*H* (2*H*) -tetrazoles and 5-amino-1-ary-1*H*—tetrazoles

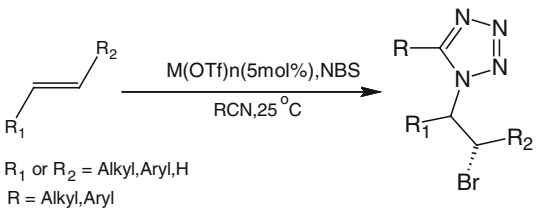


Scheme 16 Synthesis of tetrazole derivatives of naphthoquinone carboxylic acid



disubstituted oxabicyclic tetrazole in good yield (Scheme 28).

Dimroth and de Montmollin [79] described the synthesis of a number of 1,5- disubstituted tetrazoles from the action of dilute sodium hydroxide on diazoaryl mono- and di-acyl hydrazines. The procedure involved the coupling of diazonium compounds with acid hydrazides or sym-diacyl hydrazines followed by cyclization of the resulting

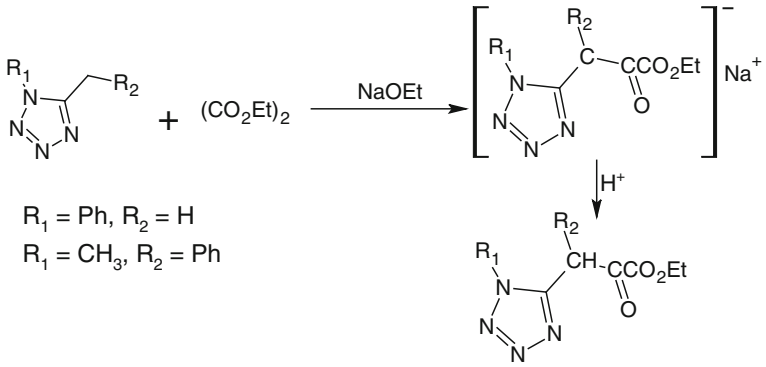


Scheme 17 Synthesis of tetrazoles via $Zn(OTf)_2$-catalyzed reaction of alkenes with NBS, RCN, $TMSN_3$

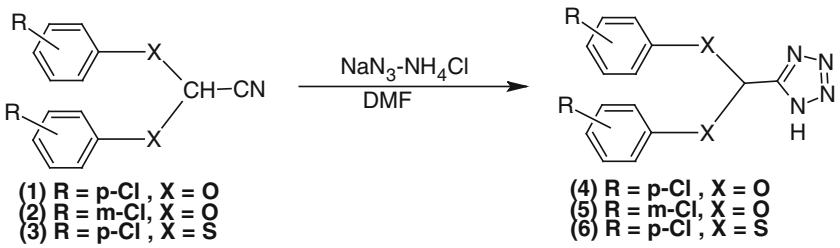
tetrazene (diazohydrazide). Using the same reaction procedure Wu and Herbst [80] reported synthesis of 1,5-disubstituted Tetrazoles from the coupling of diazonium compounds with acid hydrazides or sym-diacyl hydrazines followed by cyclization of the resulting tetrazene (diazohydrazide) (Scheme 29).

Kamijo et. al. [81] reported the synthesis of 2-allyltetrazoles by palladium-catalyzed three-component coupling (TCC) reaction of the cyano compounds, allyl methyl carbonate, and trimethylsilyl azide produces the 2-allyltetrazoles selectively in good to excellent yields (Scheme 30). Robert and Maskalerip [82] synthesized 1-isobornyl-5-alkyl tetrazoles from a series of N-isobornylalkan amides prepared from their respective nitriles and converted by the von Braun procedure to the corresponding 1-isobornyl-5-alkyl tetrazoles (Scheme 31).

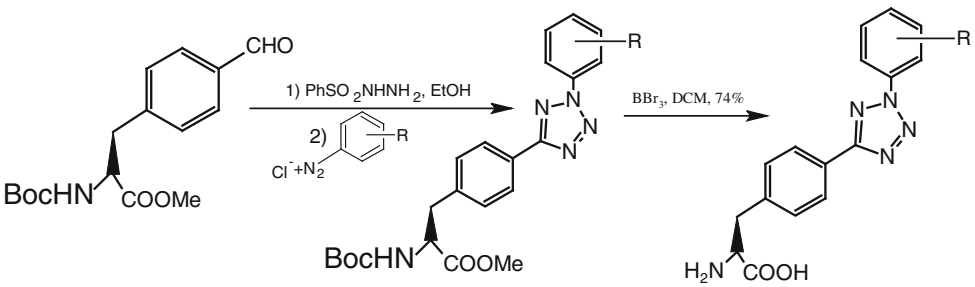
Scheme 18 Synthesis of 1,5-disubstituted *tetrazolyl pyruvate*



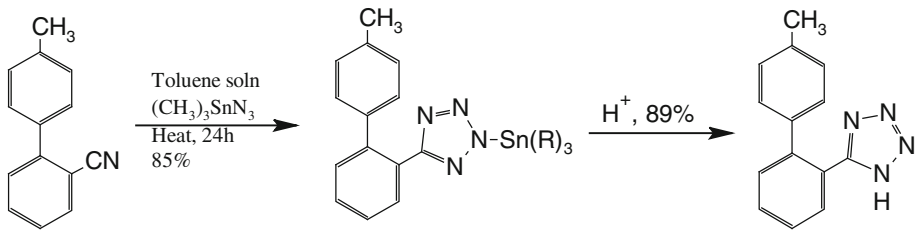
Scheme 19 Synthesis of 5-methyltetrazole derivatives



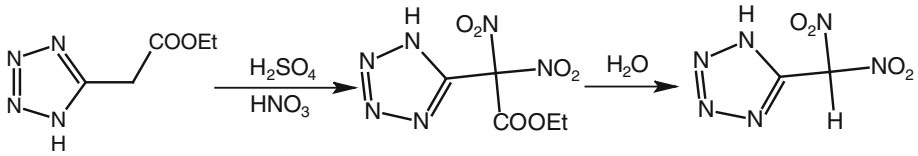
Scheme 20 Synthesis of diaryltetrazole amino acids

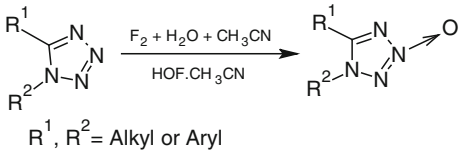


Scheme 21 Synthesis of MBT



Scheme 22 Synthesis of 5-dinitromethyltetrazole

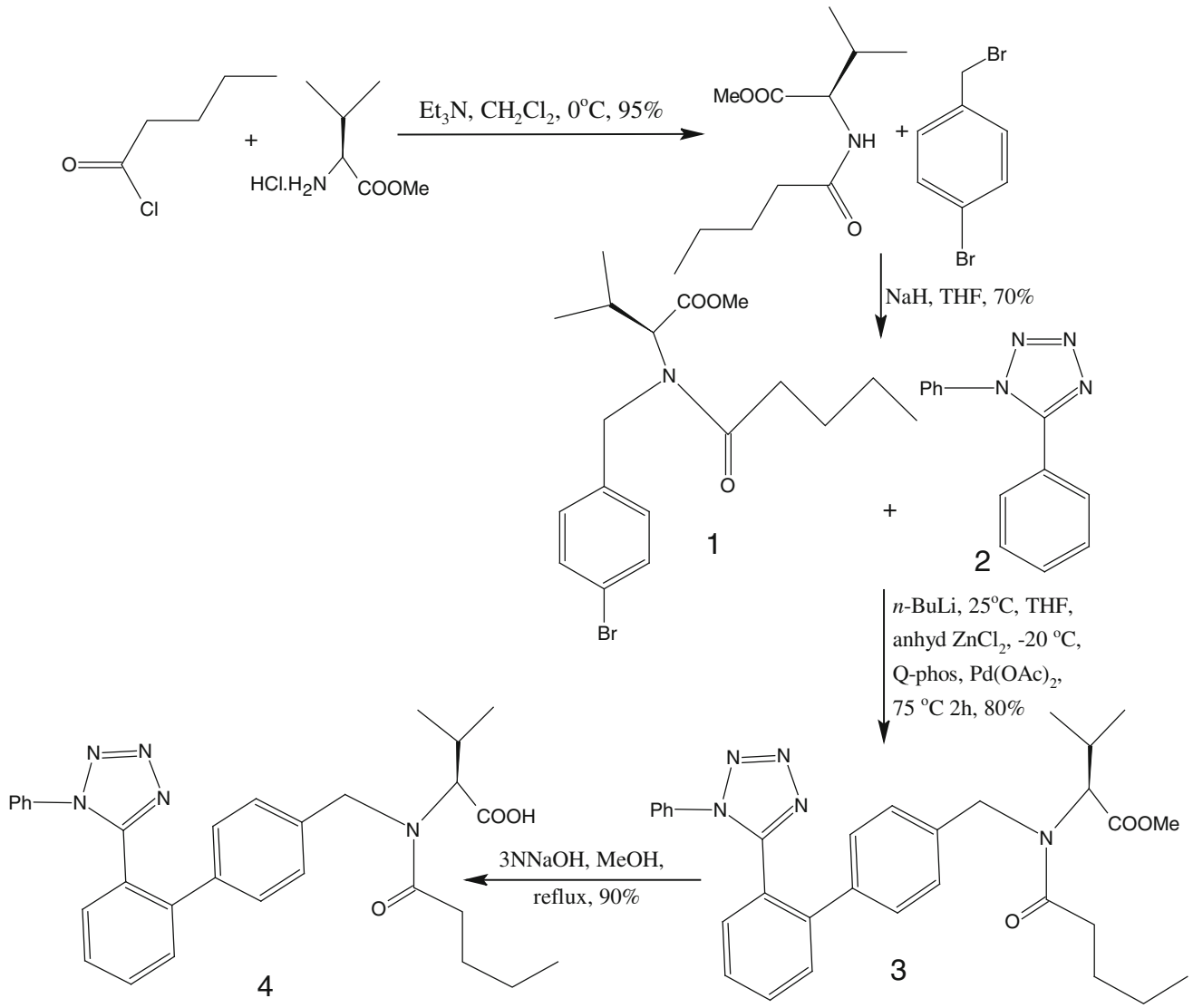




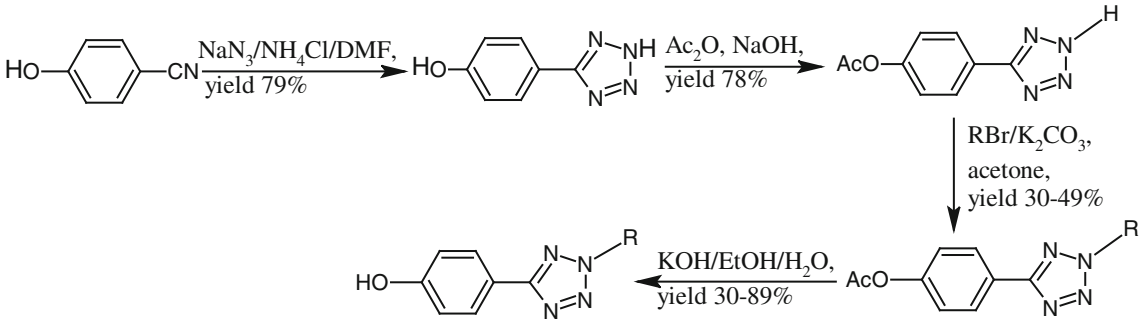
Scheme 23 The tetrazole 3-N-oxide synthesis

Kantam et al. [83] reported synthesis of 5- substituted tetrazoles by using Zn/Al hydrotalcite as an effective heterogeneous catalyst for the [2 + 3] cycloaddition of sodium azide with nitriles to afford 5-substituted 1*H*-tetrazoles in good yields (Scheme 32). The catalyst is recovered and reused for several cycles with consistent activity. Straaten et al. [84] reported synthesis of 5-substituted tetrazoles through cycloaddition of nitriles with sodium azide by using acetic acid in butanaol (Scheme 33).

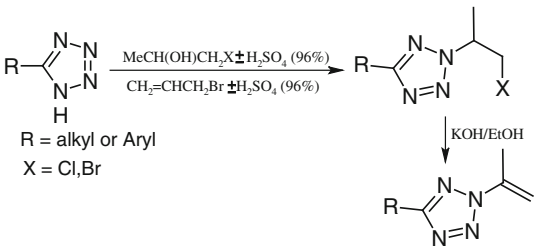
Karan and Thampi [85] synthesized 10-[(1*H*-tetrazole-5-yl)ethyl]-10H-phenothiazin by cyano ethylation of phenothiazine with acrylonitrile and triton-B followed by



Scheme 24 Synthesis of valsartan



Scheme 25 Synthesis of 5-(4-hydroxyphenyl)-2-*n*-alkyltetrazoles



Scheme 26 Synthesis of 2-(1-methylvinyl)tetrazoles

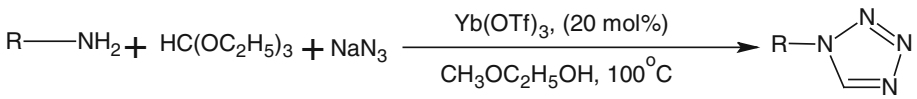
conversion of nitrile group to 1,2,3,4-tetrazoles in presence of sodium azide and ammonium chloride (Scheme 34).

Rauf and Parveen [86] report the synthesis of α-Bromo-5-methyltetrazoles derivatives through coversion of 1-phenyl ethyl undec-10-enoate, 1-phenyl ethyl (Z)-octadec-9-enoate and 1-phenyl ethyl (Z)-12-hydroxy octadec-9-enoate to their α-bromo-5-methyl tetrazoles derivatives using bromine, acetonitrile and sodium azide as reagents in excellent yield (Scheme 35).

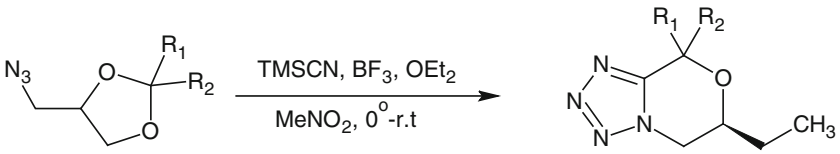
A group of workers have reported the synthesis of some unsubstituted tetrazoles from nitriles using trimethylsilyl azide in the presence of dialkylstannyl oxide [87, 88]. A mechanism for this reaction has been proposed in which trimethylsilyloxydialkylstannyl azide acts as azidizing agent (Scheme 36, Fig. 7).

Nasrollahzadeh et al. [89] have found an efficient method for the preparation of 5-substituted 1H-tetrazole derivatives, using $FeCl_3$–SiO_2 as an effective heterogeneous catalyst (Scheme 37). This method has the advantages of high yields, simple methodology, and easy work-

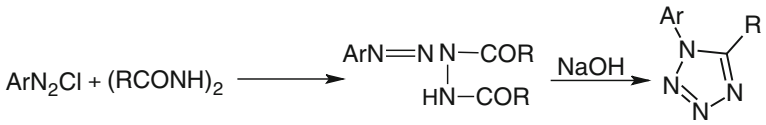
Scheme 27 Synthesis of 1-substituted 1*H*-1,2,3,4-tetrazole

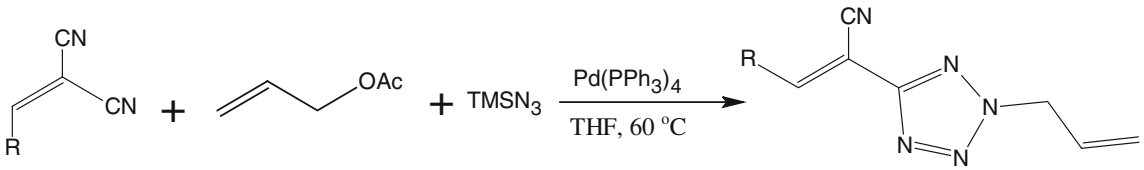


Scheme 28 Synthesis of oxabicyclic tetrazoles



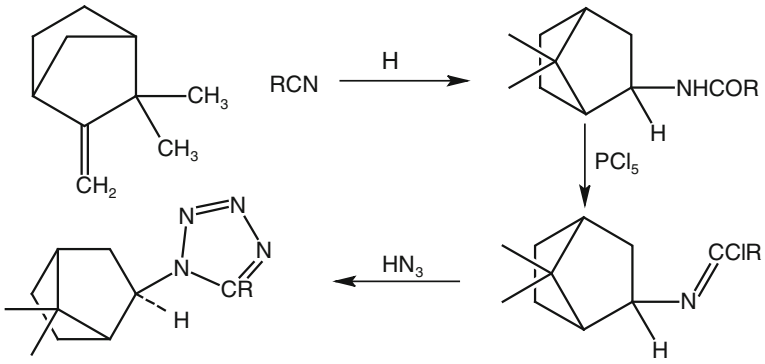
Scheme 29 Synthesis of 1,5-disubstituted tetrazoles from hydrazines



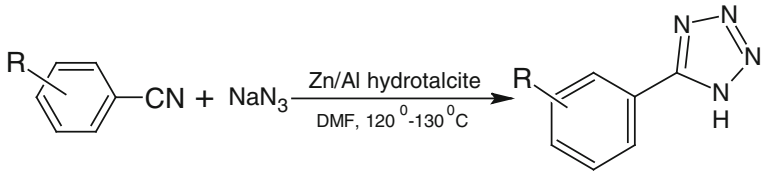


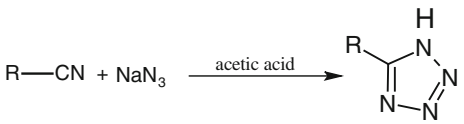
Scheme 30 Synthesis of 2-allyltetrazoles

Scheme 31 Synthesis of 1-isobornyl-5-alkyl tetrazoles



Scheme 32 Zn/Al hydrotalcite catalyzed synthesis of 5-substituted 1*H* tetrazoles



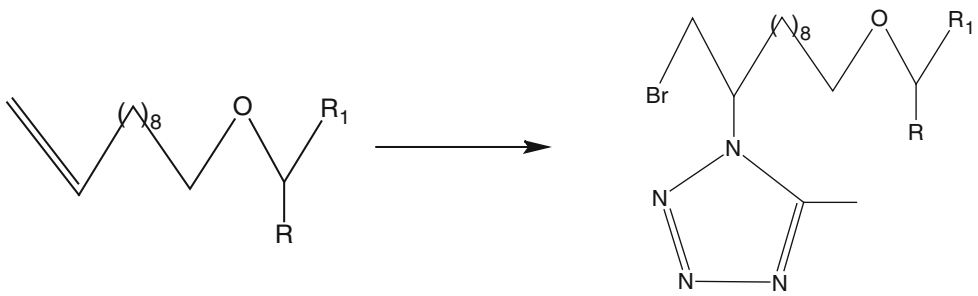


Scheme 33 Acetic acid catalyzed synthesis of 5-substituted 1*H* tetrazoles

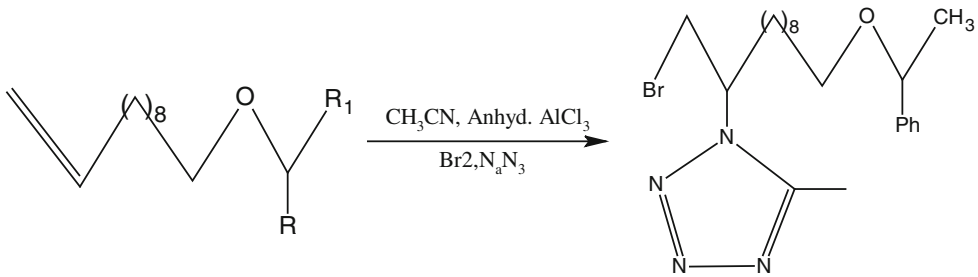
up. The catalyst can be recovered by simple filtration and reused delivering good yields.

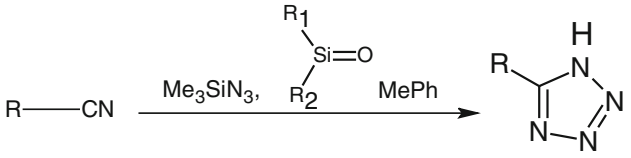
Synthesis of 5-substituted 1*H*-tetrazoles has also been achieved using tungstates as novel heterogeneous catalysts [90]. Most heterogeneous catalysts utilized for the formation of 5-substituted 1*H*-tetrazoles contain zinc as the metal core at the catalytically active site. Tungstate MWO_4 (M = Ba, Ca, Zn, Cd, Cu, Na, H) have been found to catalyze the [2 + 3] cycloaddition reaction of nitriles with sodium azide to produce 5-substituted 1H-tetrazoles in DMF (Scheme 38). The catalyst is very efficient, affording good yield of aromatic nitriles and can be reused for several cycles. The mono- and di-addition products from dicyanobenzene can be selectively synthesized, which is a development being reported for the first time. The mechanism of the catalysis may originate from the nitrile group coordinating with the unsaturated W atoms, formed by oxygen vacancies on the surface of solid tungstates. Effect of various reaction parameters has also been studied. Generally, with the catalysis of $BaWO_4$ in DMF, the

Scheme 34 Synthesis of 10-[(1H-tetrazole-5-yl)ethyl]-10H-phenothiazin



Scheme 35 Synthesis of α-bromo-5-methyltetrazoles





Scheme 36 Synthesis of unsubstituted tetrazoles using trialkylazide

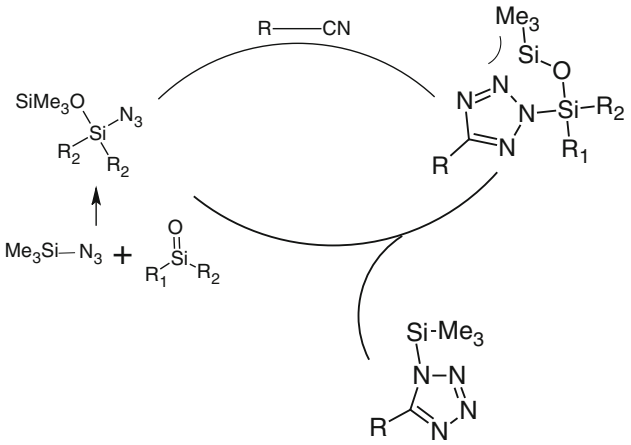
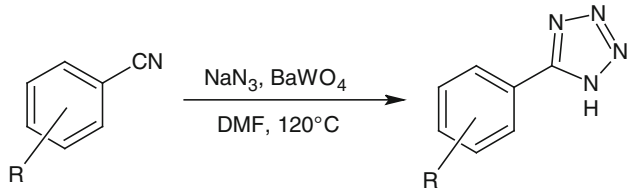


Fig. 7 Proposed mechanism of tetrazole formation using trialkylsilylazide

reaction gave moderate to good yields, whereas no products were obtained without catalytic loading. The solvent had significant effect on the catalytic performance of the $BaWO_4$ catalyst in the reaction in which DMF afforded good yield (75 %) and dimethyl sulfoxide (DMSO) moderate yield (55 %). Water and tetrahydrofuran (THF) are not suitable solvents for the reaction. The quantities of NaN_3 and catalyst used also affect the yield significantly. On using twice the amount of NaN_3, the yield increased from 27 to 75 %. However, in comparison with Zn-containing catalysts, tungstates catalysts exhibit negligible activity for alkyl nitriles [90].

Akhlaghinia and his co-workers have recently synthesized a series of of 5-substituted-1H-tetrazoles (RCN_4H) by cycloaddition reaction of different aryl and alkyl nitriles with sodium azide in DMSO using $CuSO_4{\cdot}5H_2O$ as catalyst [91]. The have reported an efficient synthetic method for the synthesis of 5-substituted-1H-tetrazoles by a successive [3 + 2] cycloaddition of various nitriles with sodium azide in the presence of a catalyst. This method is applicable to a range of nitriles including aliphatic, aromatic, and



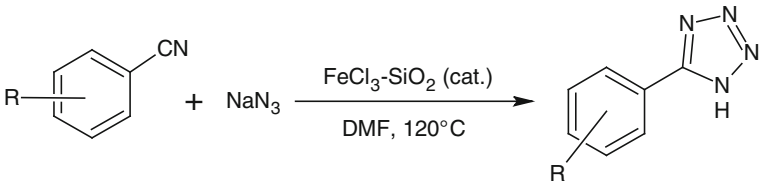
R= different substituents

Scheme 38 Synthesis of 5-substituted 1*H*-tetrazoles using tungstates as catalyst

heterocyclic nitriles. The reaction has also been performed in absence of the catalyst and reaction was not completed even after long period of time. Scheme 39 shows a plausible mechanism for the synthesis of these tetrazoles. In the beginning, coordination of nitrogen atoms of nitrile complexes with Cu(II) forms complex I which accelerates the cyclization step. Then [3 + 2] cycloaddition between the C≡N bond of nitrile compound and azide ion takes place readily to form the intermediate II. Acidic work-up, gives III and IV. The equilibrium leads to formation of the more stable tautomer IV (5-substituted 1H-tetrazole). 5-substituted 1H-tetrazoles have also been synthesized by a simple, cost effective and environmentally benign procedure by means of [2, 3] cycloaddition reaction from organic nitriles and sodium azide in glycerol under catalyst free condition [92]. A silica supported sulfuric acid catalyzed [3 + 2] cycloaddition of nitriles and sodium azide in refluxing DMF to synthesise 5-substituted 1*H*-tetrazoles is described as one the highly efficient, one-pot, protocol [93]. The protocol can provide a series of 5-substituted 1*H*-tetrazoles using silica sulfuric acid from nitriles to sodium azide in DMF in good yield.

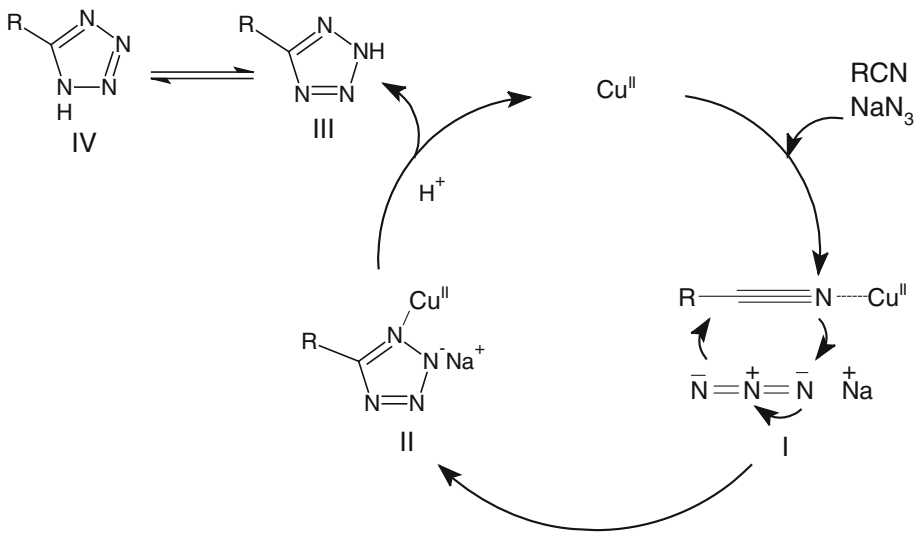
Synthesis of tetrazoles coordinated to metal ions:

A number of publications and patents describing the targeted synthesis, investigations of the structure and physicochemical properties of metal derivatives including in their structure tetrazole heterocyclic fragment has grown intensively. This is due to the wide range of practical applications of these compounds. Main applications of the tetrazole metal derivatives are as follows: organic synthesis, gas-generating compositions [94, 95]. One of the most important fields where tetrazole-containing coordination



Scheme 37 Synthesis of 5-substituted 1*H*-tetrazoles using $FeCl_3$–SiO_2 as catalyst

Scheme 39 A plausible mechanism for the formation of tetrazoles



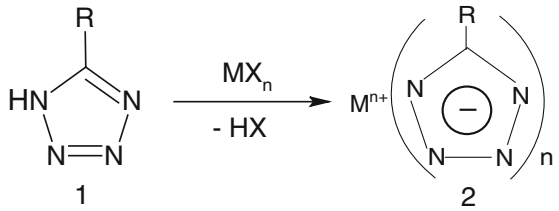
complexes are used is medical chemistry. The high physiological activity and low toxicity of tetrazoles makes it possible to regard their metal complexes as substances of versatile biochemical and pharmaceutical destination. For instance, complexes of Cu(II), Co(II), Ni(II), and Zn(II) containing in their composition as a ligand cefazolin antibiotic (in deprotonated form), show higher antibacterial activity in vitro with respect to some bacterial strains than the noncoordinated cefazolin [95–97]. Tetrazoles may be used as components of filtering materials of the new generation for the purification of biological fluids (blood, lymph etc.) from heavy metals ions [98]. Up to now a fairly large amount of material has been accumulated on the synthesis and properties of the tetrazole-containing metal derivatives.

The three main methods of synthesis of the tetrazole-containing complexes are as:

Reactions of tetrazoles with metal bases or salts

Reactions of NH-5R-tetrazoles with metal bases and salts

Over a half century the method of preparation of tetrazole-containing metal derivatives based on direct reaction of tetrazoles with metal bases or salts has been known [94, 95]. For instance, among other thermally and chemically stable azoles the NH-unsubstituted tetrazoles posses a high acidity and very low basicity [94]. In this connection, just the ability of the NH-unsubstituted 5R-tetrazoles to act as NH-acids underlies the reactivity of these compounds towards various bases (hydroxides, alcoholates, hydrides of alkali and alkaline-earth metals). This results in the formation of the corresponding salts, tetrazolates. It should be stressed that in the reactions of NH-5R-tetrazoles



M is alkali or alkaline-earth metal, n = 1, 2; X = H, OH, OAlk

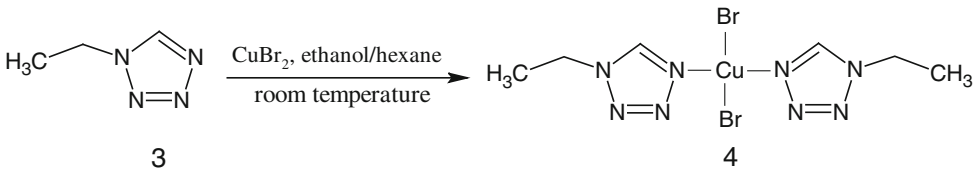
Scheme 40 Synthesis of tetrazolates (salt-like compounds)

structure 1 with hydroxides of alkali and alkaline-earth metals and as a result of the deprotonation of the tetrazole ring, these salt-like compounds possess predominantly ionic structure 2 (Scheme 40) [95]. Mainly, these reactions are carried out in aqueous medium, in ethanol or acetonitrile.

Reactions of N ^{1}-substituted tetrazoles with metal salts

N^1-Substituted tetrazoles lack the labile hydrogen atom in the ring (unlike the NH-unsubstituted tetrazoles) and therefore do not exhibit acidic properties, being only weak bases [94]. Therefore the N^1- and N^2-substituted tetrazoles are involved into the formation of metal derivatives exclusively in the neutral form [96–100]. The metal ions can bind to the nitrogen atoms of the tetrazole ring by the coordination or the covalent type. It should be noted that in the N^1-substituted tetrazoles the highest basicity is at the N4 atom; therefore, just this atom of the tetrazole ring in most cases takes part in the formation of the coordination bond. N^1-Substituted tetrazoles relatively readily enter into reactions with transition metal halides. (Scheme 41) giving adducts whose structure may be regarded as belonging to the molecular type; also many among them are polymers and precipitate from solutions forming insoluble substances [101]. The choice of a solvent for such reactions is based

Scheme 41 Synthesis of copper(II) bromide complexes of 1-substituted tetrazole



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on its electron-donor activity, the ability to dissolve the initial components, and the capability to act as a precipitating agent or the medium for crystallization of the final products. As a rule, the complex formation with N^1-substituted tetrazoles proceeds easily at room temperature in weakly coordinating solvents (alcohols, acetone, diethyl ether, acetonitrile, etc.) with the formation of a solid complex compound [95].

Reactions of N^2-substituted tetrazoles with metal salts

It was formerly believed that N^2-substituted tetrazoles are not able to enter into complexes, but recent publications disproved this stereotype. 2-Substituted tetrazoles are more sensitive to the complexing conditions, in particular, to the presence of water in the reaction mixture. Besides the formation of solid coordinated N^2-substituted tetrazoles is impeded by their good solubility. Therefore the synthesis of such complexes requires the high concentration of reagents and dry solvents; in some cases the reaction mixture should be heated and subsequently concentrated. When the N^2-substituted tetrazoles are liquid it is possible to carry out the synthesis of the metal complexes by the reaction of the starting components without solvent [95].

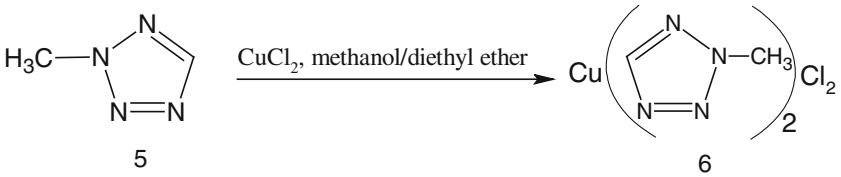
Reaction between copper(II) chloride dehydrate and 2-methyltetrazole structure 5 furnished *bis*-(2- methyltetrazole)dichlorocopper(II) structure 6 (Scheme 42) [102]. The crystallographic data showed that Cu atom environment presents an elongated octahedron with two 2-methyltetrazole ligands (N4-bounded) and two Cl atoms in equatorial positions.

Substitution of ligands for tetrazoles in coordination compounds

A method for the preparation of tetrazole containing complexes with anionic ligands consists of the substitution by tetrazole another ligand in a molecule of coordination compound (Scheme 43) [103]. This approach did not find a wide application in the synthesis of the tetrazole containing metal complexes.

Metal-promoted azidation of nitriles

A fundamentally new approach to the preparation of tetrazole-containing coordination compounds was developed in 2001 by the Sharpless team. This method was initially developed for the synthesis of 5-substituted-1-tetrazoles by simpler and more efficient procedure as compared to the classic conditions of 1,3-dipolar cycloaddition. The reaction involved inorganic azides and organic nitriles in the presence of Zn(II) salts under hydrothermal conditions (Scheme 44) [104–107].



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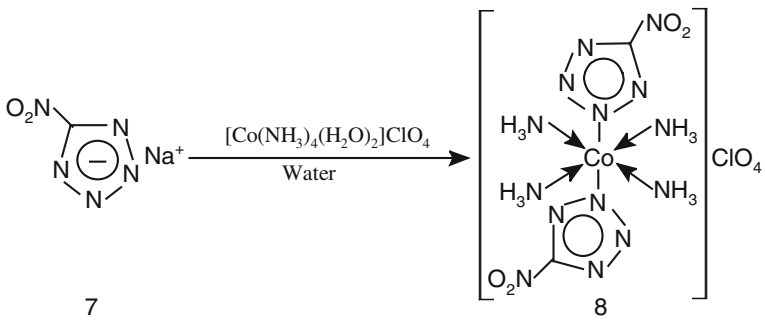
Scheme 42 Synthesis of *bis*-(2-methyltetrazole)dichlorocopper(II)

Scheme 43 Synthesis of the tetrazole containing metal complex



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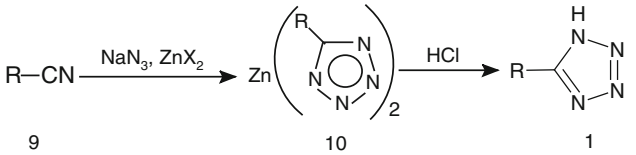


Scheme 44 Synthesis of tetrazole-containing coordination compounds

Biological importance of tetrazoles

Angiotensin II receptor antagonists

The renin-angiotensin system (RAS) plays a critical role in the regulation of blood pressure. This cascade begins with the cleavage by renin of angiotensinogen to the decapeptide angiotensin I. Subsequently, angiotensin converting enzyme (ACE) produces the powerful vasoconstrictor angiotensin II by truncating the decapeptide. Angiotensin II acts at two G-protein coupled receptors (AT1 and AT2) and it is activation of the AT1 receptor that leads to vasoconstriction. Selective antagonists of the AT1 receptor would therefore be useful as antihypertensive agents. Potent peptide AT1 antagonists have been used as pharmacological tools, but these peptides have limited therapeutic value because of their poor oral bioavailability and short duration of action. In 1982 Takeda reported a series of 1-benzylimidazole-5-acetic acid derivatives like S-8307 (IC_{50} 16 μM) to be weak but selective angiotensin II receptor antagonists [108, 109] (Fig. 8). Some workers have used molecular modelling to align S-8307 (Fig. 8) with the putative active conformation of angiotensin II. This led to the synthesis of the aryl carboxylate derivative EXP6155 (Fig. 8) which showed a significant increase in activity over the lead (IC_{50} 1.6 μM), but did not show any antihypertensive effect when dosed orally. From this starting point a series of progressively more potent compounds were synthesised, exemplified by the synthesis of EXP7711 (Fig. 8) which produced another enhancement of binding affinity (IC_{50} 0.23 μM) and was shown to be orally active [110].

The biphenyl carboxylic acid EXP7711 was found to be more active upon *i.v.* dosing (ED_{30} = 3 mg/kg) than oral dosing (ED_{30} = 11 mg/kg). In an effort to find compounds with greater potency and oral bioavailability a series of carboxylic acid bioisosteres were prepared. From this starting point the orally active biphenyl tetrazole AT1 receptor antagonist DuP 753 (Losartan) (Fig. 8) was developed. Losartan exhibits greatly improved binding affinity (IC_{50} 0.02 μM) and, more importantly, better oral potency (ED_{30} 0.8 mg/kg) [111]. The authors felt that the increase in receptor binding was due to the greater ability of the tetrazole to distribute a negative charge at physiological pH, allowing for better interaction (vs. carboxylate EXP7711 with the positive charge in the receptor. It is interesting to note the logP differences between the carboxylate EXP7711 and tetrazole (Losartan), illustrating the increase in lipophilicity of the tetrazole heterocycle, whilst the p*K*a of the two compounds remained comparable. The

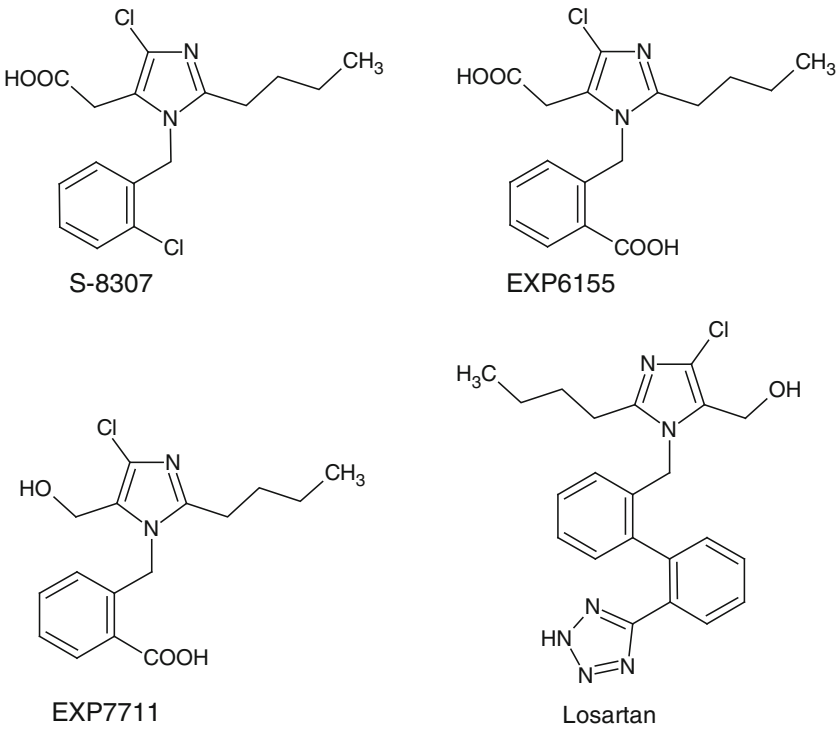


Fig. 8 Novel imidazole derivatives

major metabolite of Losartan is the *N*2-glucuronide, which has been implicated in the long duration of action, perhaps by an enterohepatic reprocessing mechanism [112]. Losartan has an oral bioavailability of about 33 % in humans and is rapidly absorbed (peak plasma levels in 1 h) and in 1995 Losartan was approved by the FDA for clinical use. Since the disclosure of Losartan and related structures the biphenyl tetrazole moiety has been incorporated in a wide variety of AT1 receptor antagonists [112].

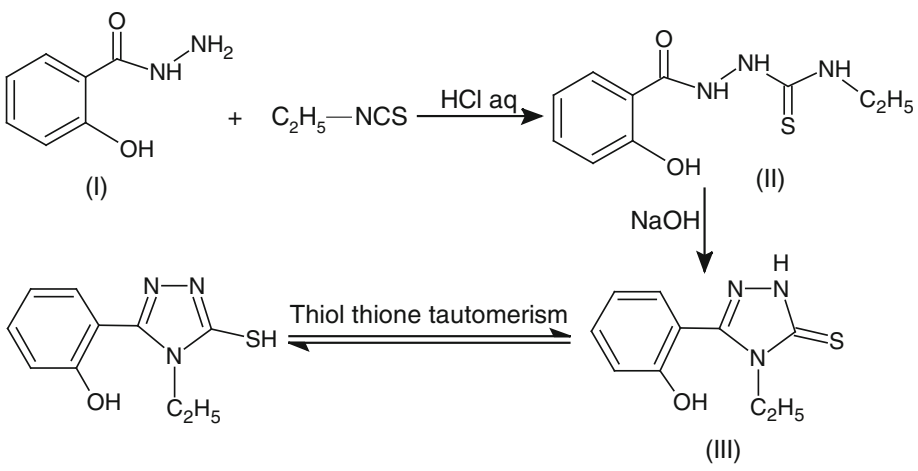
The tetrazole group is similar to the carboxylic function in terms of size and acidity but is apparently more stable metabolically; its use as a carboxylic acid mimic in analogues of biologically active compounds has therefore attracted increasing interest [113]. Such derivatives often exhibit different potencies and selectivities in their pharmacological profiles as compared with their carboxylic counterparts. The discovery by researchers at DuPont [114, 115] of a promising non-peptide angiotensin receptor antagonist containing a 5-aryltetrazole moiety (Dup 753) is only one of many examples arising from the impressive amount of work on these derivatives as can be judged by the number of publications, especially in the patent literature, that have appeared in the past few years.

Antimicrobial activity

Tetrazole ring is associated with potential antibacterial and antifungal activities [116–119]. Some 5-substituted tetrazole derivatives have revealed strong growth inhibitory activity against *Candida* species [120]. In an attempt to find new antifungal agents in the tetrazole series another group of workers have found some 1-(2,4-dihydroxyl thiobenzoyl)-tetrazoles as potential antifungal agents [121]. Rostom et al. [122] have obtained some azole antimicrobial pharmacophore-based tetrazoles as potential antimicrobial agents. These compounds were able to display variable growth inhibitory effects on the tested *Gram positive* and *Gram negative* bacteria with special efficacy against the Gram positive strains. Meanwhile, some compounds exhibit moderate antifungal activity against *Candida albicans* and *Aspergillus fumigatus*. Encouraged by the various biological activities of tetrazole and its derivatives, Dhayanithi and his coworkers carried out the synthesis of a novel series of 5-thio substituted tetrazole derivatives and visualize their antibacterial and antifungal properties [123]. In another recent investigation the synthesis of some tetrazole derivatives was carried out and these compounds were screened for their antiamoebic and cytotoxic properties [124]

According to Koparir et al. [125] synthesis of 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione (III) (Scheme 45), the antimicrobial study revealed that this molecule shows very high antibacterial and antifungal activities against pathogenic strains. Apart from antimicrobial studies, 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione also showed very high antioxidant activity as the scavenging activity increases with increasing sample concentration in the range tested.

The investigation of antibacterial and antifungal screening data revealed that the 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione showed good inhibition at 1.56–25 mg/mL in DMSO. The screening result indicates that 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione tested exhibited significant antibacterial and antifungal activities when compared with the reference drug (Ciprofloxacin, Ciclopiroxolamine). The title compound was found to be same potent as the reference drug, ciprofloxacin, in case of *Escherichia coli.* Structure and biological activity relationship of title compound showed that presence of 4-hydroxy groups attached to phenyl ring to the triazole ring of the title compound is responsible for good antimicrobial activity [126]. The study showed that

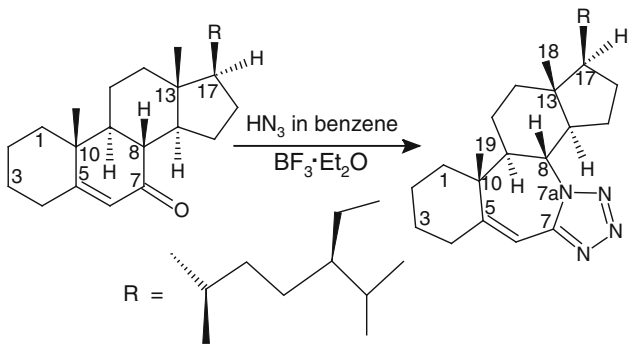


Scheme 45 Synthesis of 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione (III)

the synthesized compound can be used as template for future development through modification and derivatization to design more potent and selective antimicrobial agents.

Since the antioxidants are gaining a lot of importance as panacea for a large number of life-style diseases like aging, cancer, diabetes, cardiovascular and other degenerative diseases, it is of immense significance to establish some new antioxidants by a convenient synthetic methodology. Although a number of methods such as ORAC, ABTS, DMPD, FRAP, TRAP, TBA, superoxide radical scavenging, hydroxyl radical scavenging, nitric oxide radical scavenging, xanthine oxidase, cytochrome C, reducing power method, etc. available, the DPPH method is very common and proved as the best [127]. It has been reported that the antioxidant activity of the phenolic compounds depends on their molecular structure, especially on their hydrogen-donating ability and subsequent stabilization of the formed phenoxy radical [128]. 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione has scavenging activity between 40.9 and 88.1 % within the investigated concentration range. The antioxidant activity of the 4-ethyl-5-(2-hydroxyphenyl)-2H-1,2,4-triazole-3(4H)-thione is obvious that the scavenging activity increases with increasing sample concentration in the range tested. This activity can be explained on the basis of their structure as these derivatives posses phenolic hydroxyls which are available as hydrogen donors to the DPPH radical.

The compound 7a-Aza-B-homostigmast-5-eno [7a, 7-d] tetrazole was tested against two human cancer cell lines: HCT116 and HepG2 and one non-cancerous HFL1 (human lung fibroblast) cell line (Scheme 46) [129]. The IC_{50} values for these compounds were compared to doxorubicin. The results indicate that the compound inhibits various cancer cell lines in a dose-dependent manner. The antitumor efficacy of the compound may be attributed to its ability to deactivate ribonucleotide reductase, the enzyme that catalyzes the conversion of ribonucleotides to deoxyribo-nucleotides. As a consequence, the compound interferes with DNA synthesis, thus decreasing the rate of replication of tumour cells and inhibiting tumour growth. The antitumour activity seems to be due to an inhibition of DNA synthesis in cancer cells produced by modification in reductive conversion of ribonucleotides to deoxyribonucleotides [130]. The antibacterial screening [129] showed moderate to good inhibition. The screened compound was found to have good zones of inhibition. The highest activity in case of Gram positive bacteria was observed against *Corynebacterium xerosi* against the reference drug ciprofloxacin with MIC equal to 0.078 mg/mL. Similarly, the highest activity in the case of Gram negative bacteria was found for *Proteus vulgaris* in comparison with the standard drug, gentamicin with MIC equal to 0.019 mg/mL.



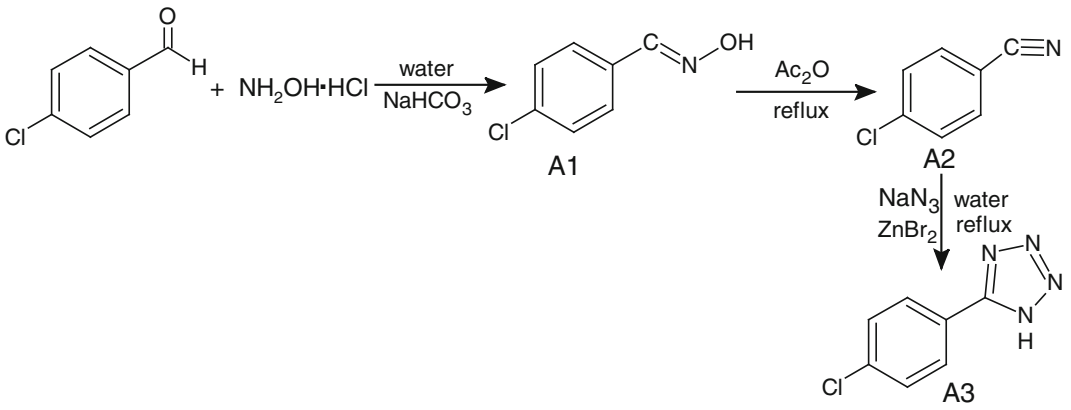
Scheme 46 Synthesis of the 7a-Aza-B-homostigmast-5-eno [7a,7-d] tetrazole

We have recently synthesised tetrazole ring bearing acyl-hydrazones and were screened for their in vitro antifungal activity [131]. These target compounds were obtained in a five step reaction procedure as outlined in Schemes 47 and 48. The mechanism of their antifungal activity was assessed by studying their effect on the plasma membrane using flow cytometry and determination of the levels of ergosterol, a fungal-specific sterol. Our results showed that the results also showed that the presence and position of different substituents on the phenyl ring of the acylhydrazone pendant seem to play a role on the antifungal activity as well as in deciding the fungistatic and fungicidal nature of the compounds.

Present study was undertaken to synthesize some novel tetrazole ring bearing acyl-hydrazone derivatives to investigate their probable antifungal effects. Target compounds were obtained in a five step reaction procedure as outlined in Schemes 47 and 48. First of all, 5-(4-chlorophenyl)-1*H*-tetrazole was synthesized from 4-chlorobenzonitrile. 4-chlorobenzonitrile in turn was obtained from 4-chlorobenzaldehyde, via an oxime intermediate. In the fourth step 2-[5-(4-chlorophenyl)-1*H*-tetrazol-1-yl] acetohydrazide (A5) was prepared from 5-(4-chlorophenyl)-1*H*-tetrazole (A3). The acyl-hydrazone derivatives (TH1–TH10) were obtained through a condensation reaction of 2-[5-(4-chlorophenyl)-1*H*-tetrazol-1-yl]-acetohydrazide (A5) with different aromatic aldehydes in ethanol medium in 1:1 molar ratio.

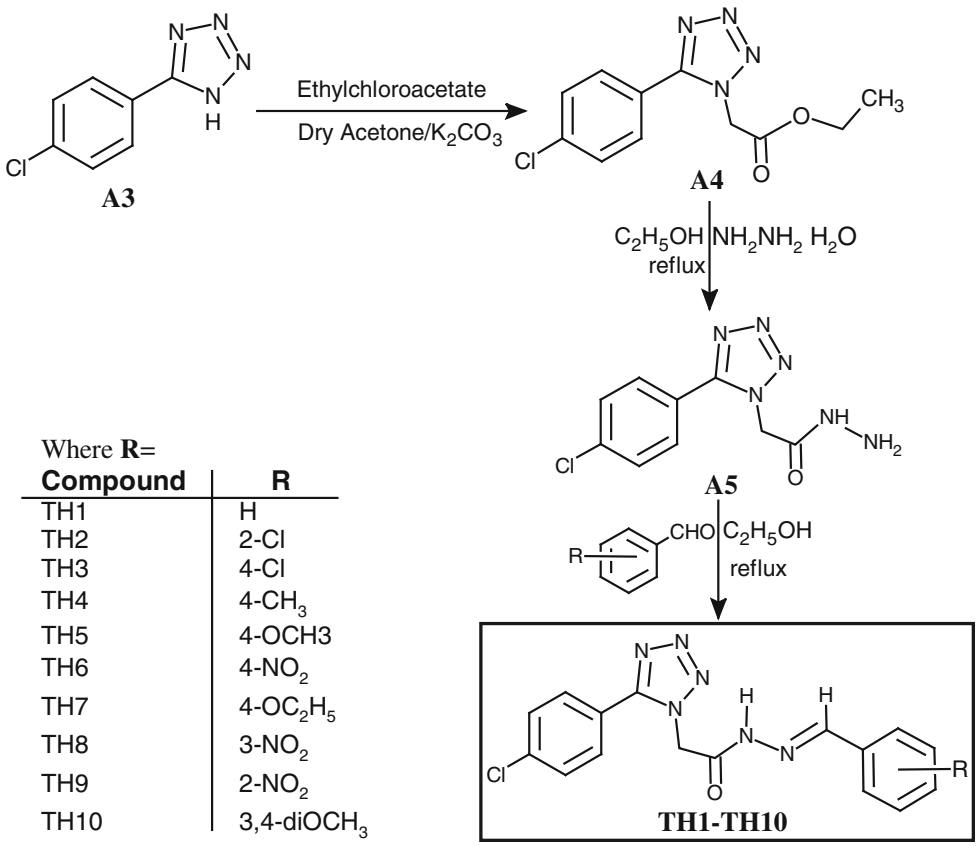
Miscellaneous

Straaten et al. [84] have synthesized tetrazole analogue of nicotinic acid which is effective in high concentrations as a growth factor for *Lactobacillus arabinosus* and was found to be three to four times more potent than nicotinic acid in lowering serum cholesterol in man. Tetrazole analogue of a series of N-Phenyl anthranilic acids have been reported to



Scheme 47 Synthesis of 5-(4-chlorophenyl)-1*H*-tetrazole (**A3**)

Scheme 48 Schematic representation of synthesis of target compounds (TH1–TH10)



Where **R**=

Compound	R
TH1	H
TH2	2-Cl
TH3	4-Cl
TH4	4-CH_3
TH5	4-OCH3
TH6	4-NO_2
TH7	4-OC_2H_5
TH8	3-NO_2
TH9	2-NO_2
TH10	3,4-diOCH_3

possess anti-inflammatory activity in both pharmacological and clinical tests [132, 133]. Tetrazoles are also reported to exhibit antihypertensive antiallergic and antibiotic activity. Furthermore aminotetrazole derivative have been patented for their muscle relaxation, anti-inflammatory, antiarthritic, analgesic, ulcer therapeutics and cocediostatic properties [134–136]. Tetrazole are used as plant growth regulators herbicides and fungicides in agriculture as stabilizers in photography and photoimaging and as explosives in rocket propellants. Some of the 1-substituted 1,2,3,4-tetrazole compounds have shown strong phytocidal activity [77]. A series of perfluoro amides having 1*H*-1,2,4-tetrazole moiety as an acidic heterocycle have been reported to display highly significant insulin sensitizing property and thereby exhibit potent hypoglycemic activity [137]. In addition some compounds bearing a 1*H*-tetrazole moiety in there skeleton have been found to be potent antihyperglycemic agents [138]

Conclusion

Various successful attempts have been undertaken to make the amendment in the structures of the effective azole drugs in order to improve their antimicrobial potency and selectivity. However, few reports have discussed the contribution of the tetrazole moiety in such pharmacophore in spite of the potential biological activities encountered with some tetrazoles. In this review we discussed the various synthetic methods used to synthesize tetrazoles and some of their biological properties, with the aim to focus the attention of researchers towards this neglected moiety, which if explored can prove to be biologically more important than it is today.

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