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REVIEW ARTICLE

Recent Synthetic Strategies for Monocyclic Azole Nucleus and Its Role in Drug Discovery and Development

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Abstract: ***Background*:** In recent years, the development and diversification of heterocyclic compounds has become central to the discovery of bioactive compounds with novel or improved pharmacological properties. In particular, *N*-containing heterocycles are proved to be promising leads and drug candidates, and received huge attention of the medicinal chemists.

***Objective*:** Many drugs especially antibiotics are becoming obsolete due to the development of multidrug resistance. Moreover, toxicity and other side effects of some drugs necessitated the quest for safer and more potent drug candidates. The current review article described biological potential of various monocyclic azoles. Recent developments in the synthesis of azole derivatives have been also reviewed.

***Conclusion*:** The presence of *N*-heterocyclic rings can influence the pharmacokinetics, pharmacodynamics, pKa and bioavailability profile of the drug molecules. Compounds containing monocyclic azole rings showed various biological activities and number of molecules are in clinical practice. A number of important leads and potential drug candidates containing azole nucleus are in advance stages of drug developments. Thus, simple, atom economic and more efficient synthetic strategies are desired for the synthesis of new libraries of the compounds.

Keywords: Azole, heterocycles, pyrrole, pyrazole, imidazole, triazole, tetrazole, pentazole, synthetic strategies.

1. INTRODUCTION

Heterocyclic ring represents an important structural unit of various drugs. The scaffold is widely distributed in natural products, biologically active molecules, vitamins besides their role in agrochemicals. Heterocyclic rings are also components of most important biomolecules essential to life such as DNA and RNA. In fact more than 95% of the pharmaceuticals comprises of heterocyclic core [1]. Amongst various heterocycles, *N*-containing heterocyclic compounds have attracted huge attention due to their numerous biological potential. For instance, a number of natural drugs such as papaverine, quinine, atropine, morphine, reserprine, including essential amino acids like proline, tryptophan, histidine etc. contain *N*- heterocyclic core in their structure. Moreover, this core is also present in various vitamins such as vitamin B1 (Thiamin), vitamin B2 (Riboflavin), vitamin B3 (Nicotinamide) *etc*. Two classes of azoles *viz*: imidazoles (clotrimazole, ketoconazole, miconazole *etc*.) and triazoles (fluconazole, itraconazole, terconazole, posaconazole *etc*.) are already in clinical use for the treatment of various fungal infections. Similarly, pyrrole a class of azole is an important unit of macrocyclic core/porphyrin ring of oxygen carrier protein hemoglobin, photosynthesizing pigment chlorophyll *etc*. In this review article, we have exclusively highlighted monocyclic azoles (containing only *N* atom in the ring), their biological potential including drugs in clinical practice. The article also describes some recent developments in the synthesis of monocyclic azoles. This review article would help in generating new thoughts for the design and discovery of various pharmaceutical agents incorporating monocyclic azole core as active functional pharmacophore.

2. CLASSIFICATIONS OF AZOLES

2.1. Azole

The azoles are five-membered heterocyclic compounds containing nitrogen as a part of the ring. The ring may contain more than one nitrogen atoms (Fig. **1**, Type 1) and/or other heteroatom such as sulphur and oxygen (Fig. **1**, Type II). The fusion of a carbocyclic or heterocyclic ring with five membered core aromatic ring structure further enriches the chemical diversity of azoles leading to biologically useful classes of compounds like Indole, benzoxazole, benzothiazole *etc*. (Type III).

In this review article, we have highlighted only monocyclic azoles of Type 1 *i.e*. five-membered heterocyclic compounds which contain one or more than one nitrogen in the ring system. Depending on the number of nitrogen atoms and their position in the ring, monocyclic azoles of Type 1 can be further classified into five subclasses (Fig. **2**).

3. MONOAZOLE (PYRROLE)

The simplest monocyclic azole containing only one nitrogen atom is pyrrole. In 1834, it was detected by Runge and isolated by

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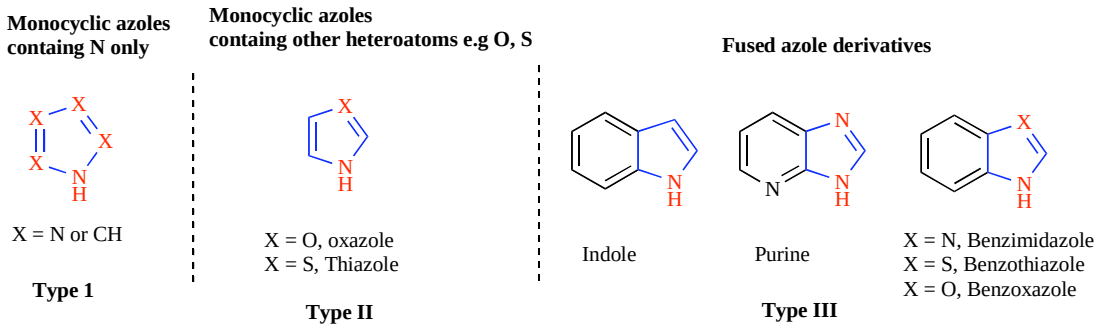


Fig. (1). Various classes of azole derivatives.

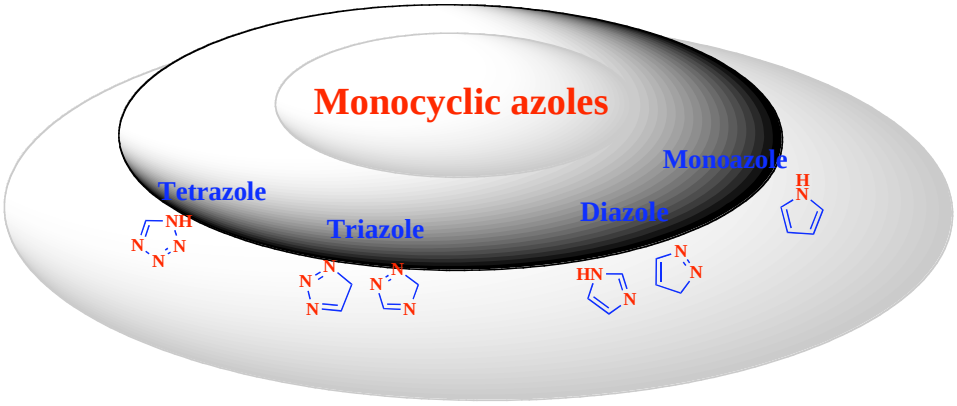
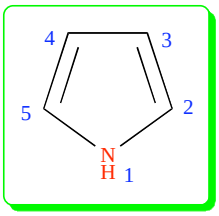


Fig. (2). Classes of Monocyclic azole.

Anderson in 1857 as a pyrolysis product of bone material [2]. Diversely substituted pyrroles have shown various biological activities such as HIV fusion inhibitors, antibacterial, anti-inflammatory, antioxidant and antifungal, besides its relevance in material science. For instance, one of the best-selling drug atrovastatin (marketed under the trade name Lipitor) contain pyrrole substructure. Similarly, non-steroidal anti-inflammatory drug tolmetin (marketed as Tolectin) and anticancer agent tallimustine comprises of pyrrole unit. Moreover, it is an important structural component of many natural products *e.g.* macrocyclic porphyrin ring of heme, chlorophyll, chlorin, bacteriochlorins *etc*. The classical methods for the synthesis of pyrroles ionncluding Knorr, Paal-Knorr, Hantzsch, etc. have been developed a century ago and have been extensively reviewed by various authors. To improve the atom economy, experimental simplicity besides use of easily available starting materials, various modifications/improvements in the existing classical protocols have been carried out. Some current strategies for the construction of pyrrole core have been described in Fig. (**3**).



Pyrrole

From the viewpoint of green chemistry, catalyst recyclability is an important issue for the design of synthetic strategies. Recently, synthesis of pyrrole derivatives have been accomplished from the reaction of diphenyldiacetylene with different amines in the presence of CuCl(I) as catalyst in DMF (route-a) [3]. The synthesis of pyrroles with various aromatic substituents was accomplished from a butadiene derivative under microwave irradiation at 65^{o}C for 15 min in Tetrahydrofuran (THF) (route-b) [4]. Also, the reaction of beta-enamino ketones with aryl acetylenes in the presence of I_2 (1.5equiv) and K_2CO_3 (1equiv) in DMSO at 100^{o}C for 6h in open air gave substituted pyrroles (route-c) [5]. In 2016, the enaminones of both aromatic and aliphatic amines reacted easily with arylglyoxals resulting in pyrrole derivatives, but the enaminones of ethyl acetoacetate led to complex mixtures and no pure product could be isolated (route-d) [6]. Bhakta *et al.* synthesized pyrrole derivatives through a microwave assisted Paal-Knorr reaction (route-e) [7]. Similarly, various pyrroles were synthesized using equimolar amounts of starting compounds in an open Pyrex vessel and irradiated in a microwave oven, in the presence of boron trifluoride diethyl etherate (10 mol%) in dichloromethane for 10–16 min (route-f) [8]. Farahi *et al.* used silica sodium carbonate (SSC) as the catalyst for the reaction of α-aminoketones with dimethyl acetylenedicarboxylate to produce pentasubstituted pyrroles derivatives (Route-g) [9]. The starting material i.e α-aminoketones were prepared by the reaction of benzoin derivatives and aromatic amines using a catalytic amount of silica tungstic acid. Importantly, the SSC catalyst could be recycled and successfully used for three consecutive runs without any significant loss in the activity. In an improved version, Wang *et al.* (2015) used lactic acid as a bio-based green solvent for the condensation reaction of α-amino carbonyl compounds with 1,3-dicarbonyl compounds furnishing pyrrole derivatives (route-h) [10].

3.1. Biological Activities of Monoazoles

Monoazoles have shown various biological activities such as antibacterial, anti-inflammatory, analgesic, anti-tumor, anti-epileptic, antiviral, hypotensive, anti-diabetic and anti-microbial activities (Table **1**).

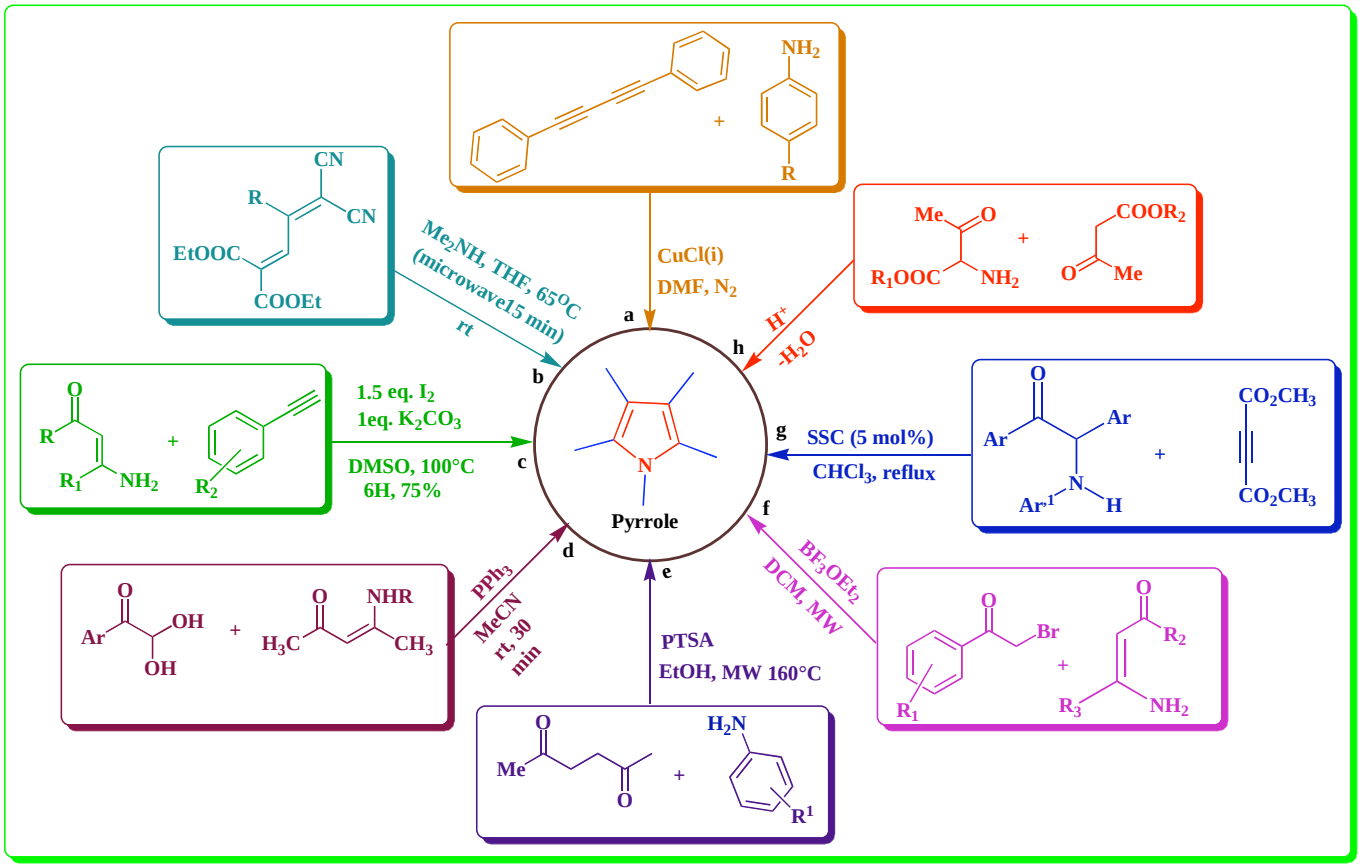


Fig. (3). Different routes for the synthesis of substituted pyrroles. A number of green methods have been developed that include use of microwave and solvent less conditions for the synthesis of pyrrole derivatives.

Table 1. Drugs in clinical practice containing a monoazole nucleus.

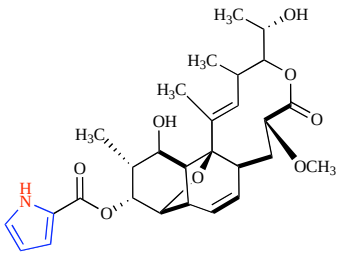
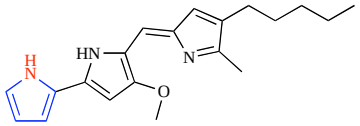
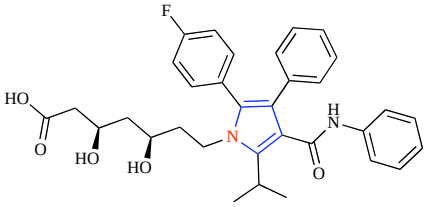
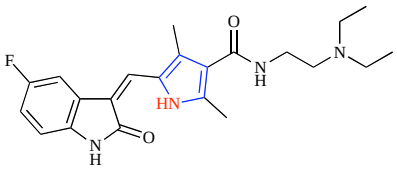
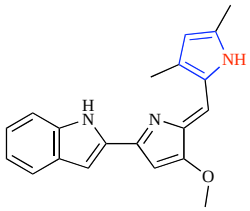
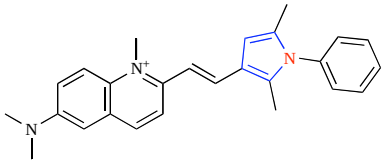
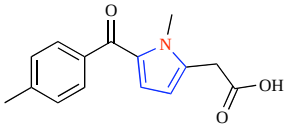
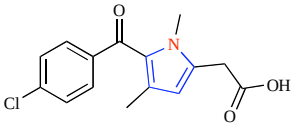
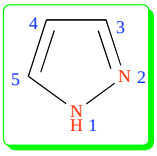
Activity	Name	Structure and Chemical Name	Mechanism of Action	Use	Reference
ANTIBACTERIAL	Nargenicin A_1	 (7R,8aS,10aR,11S,12R,13R,14R,14aS,14bS,E)-14-hydroxy-4-((S)-1-hydroxyethyl)-7-methoxy-1,3,13-trimethyl-6-oxo-3,4,6,7,8,8a,10a,11,12,13,14,14a-dodecahydro-11,14b-epoxynaphtho[2,1-e]oxecin-12-yl 1H-pyrrole-2-carboxylate	Inhibits cell proliferation and induces HL-60 cell differentiation when administered in Combination with 1,25-(OH)2D3 or ATRA	Neoplastic disease	[11-13]
	Prodigiosin	 4-methoxy-5-[(Z)-(5-methyl-4-pentyl-2H-pyrrol-2-ylidene)methyl]-1H,1'H-2,2'-bipyrrole	pH modulator, cell cycle inhibitors, DNA cleavage and mitogen activated protein kinase regulators (MAPK)	Lyme disease	[14-18]

Table 1. contd…

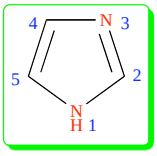
Activity	Name	Structure and Chemical Name	Mechanism of Action	Use	Reference
	Atorvastatin	 (3R,5R)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid	HMG-CoA reductase inhibitor, inhibits rate-limiting step in cholesterol biosynthesis by competitively inhibiting HMG-CoA reductase	Hyperlipidaemias	[19-21]
ANTICANCER	Sunitinib	 N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide	Multi kinase inhibitor (including VEGF and PDGF receptor tyrosine kinases) some of which are implicated in tumor growth, angiogenesis and metastasis	Renal cell carcinoma	[22-24]
	Obatoclax	 2-(2-((3,5-Dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-1H-indole	Inhibitor of the BCL-2 family of proteins. This inhibition induces apoptosis in cancer cells, preventing tumor growth	Leukemia, lymphoma, myelofibrosis and mastocytosis	[25-28]
ANTHELMINTICS	Pyrvinium	 2-[(E)-2-(2,5-Dimethyl-1-phenylpyrrol-3-yl)ethenyl]-N,N,1-trimethylquinolin-1-ium-6-amine	Inhibit WNT signaling *via* activation of casein kinase 1α(CK-1α-a key kinase that phosphorylates β-catenin for degradation)	Infection such as threadworm, seat worm, pinworm	[29-31]
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	Tolmetin	 [1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetic acid	Inhibit cyclooxygenases (COX) enzymes Prostaglandin synthetase inhibitor	rheumatoid, juvenile and osteoarthritis disease	[32]
	Zomepirac	 2-[5-(4-chlorobenzoyl)-1,4-dimethyl-pyrrol-2-yl]acetic acid	Inhibit cyclooxygenases (COX) enzymes Prostaglandin synthetase inhibitor	Myositis, traumatic, osteoarthritis	[33]

4. DIAZOLES

The two isomers of diazole are pyrazole and imidazole, also known as 1, 2-diazole and 1, 3-diazole respectively. Both of these have been discussed separately.



Pyrazole (1,2-Diazole)



Imidazole (1,3-Diazole)

4.1. Pyrazole or 1, 2-diazole

A number of synthetic procedures have been reported for the synthesis of pyrazole and some of the latest developments are illus-

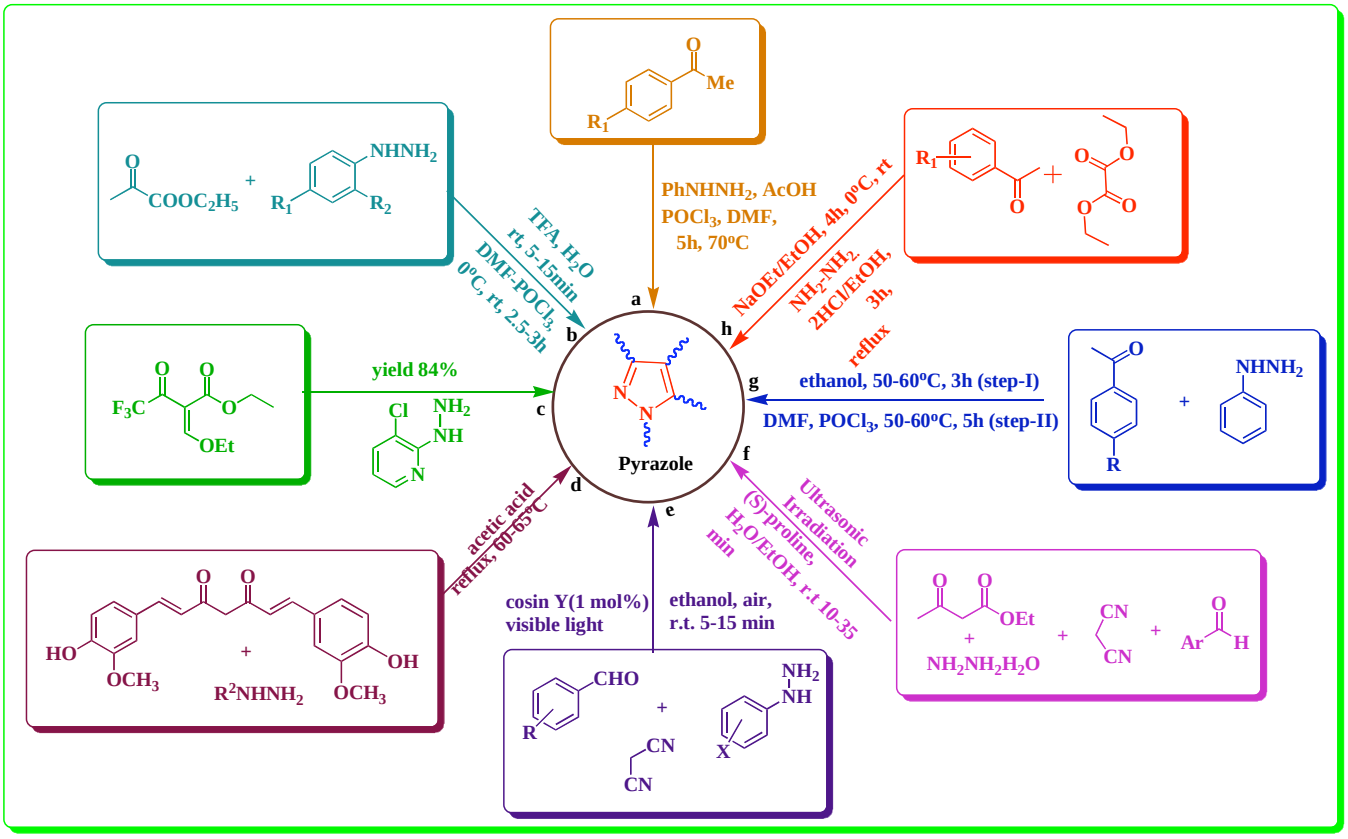


Fig. (4). Different routes for the synthesis of substituted diazoles (Pyrazole), a number of reagents and catalysts have been used to get the improved yield of the diazoles. Green tools of organic synthesis like ultrasound irradiations has also been used.

trated in Fig. (**4**). Many substituted pyrazole derivatives are reported to possess a wide array of biological activities such as antimicrobial, antidepressant [34], anticancer, anti-inflammatory etc. besides their role as chelating and extracting reagents in organic synthesis.

4.1.1. Synthetic Strategies

In 2016, synthesis of pyrazole derivatives has been reported through the reaction of ketones with phenylhydrazine using AcOH followed by cyclization and subsequent formylation of the resulting hydrazones with the Vilsmeier-Haack reagent ($POCl_3$/DMF) (route-a) [35]. Synthesis of pyrazole derivatives was reported *via* two step synthetic process wherein in the first step ethylpyruvate reacted with phenyl hydrazine in the presence of trifluoroacetic acid in water for 5-15 min to yield intermediates and in the second step these intermediates react with DMF-$POCl_3$ (route-b) [36]. Liu *et al.* reported the synthesis of pyrazole derivatives by the reaction of 3-chloro-2-hydrazinylpyridine and ketone ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (route-c) [37]. Similarly, synthesis of pyrazole derivative was achieved by the reaction of curcumin (5mmol), and hydrazines (5mmol) in acetic acid at 60-65 ^{o}C (route-d) [38]. In 2015, Yadav *et al.* reported atmospheric oxygen mediated synthesis of pyrazoles using visible irradiations (route-e) [39]. Khoobi *et al.* (2015) reported one-pot four component reaction of ethyl acetate, hydrazine hydrate, malononitrile and 4-methylbenzaldehyde in the presence of (S)-proline in water-ethanol under reflux. Ultrasonic irradiations were used as an alternative mode of energy to accelerate the reaction and improve the yield (route-f) [40]. In 2015, synthesis of pyrazole derivatives was reported in two steps involving condensation of the acetophenones with phenyl hydrazines in ethanol to produce phenyl hydrazones and then its cyclization *via* Vilsmeir-Haack reaction (route-g) [41]. Kamal *et al.* reported the reaction of acetophenones with diethyl oxalate in the presence of sodium ethanolate in ethanol followed by cyclization with NH_2-NH_2.2HCl in ethanol to produce pyrazole derivatives (route-h) [42].

4.2. Imidazole or 1, 3-diazole

Imidazole or 1,3-diazole is a planar, amphoteric, colorless solid and is soluble in water. Imidazole is an important structural unit in the biologically important molecules such as histidine, histamine etc. Moreover, drugs such as nitromidazole (antibiotic) and midazolam (sedative) contain imidazole ring as active pharmacophore in their structure. In addition, imidazole is a vital constituent of imidazolium based ionic liquids, *N*-heterocyclic carbene complexes and as a ligand it finds applications in coordination chemistry.

4.2.1. Synthetic Strategies

Some of the important synthetic strategies for the construction of imidazole ring and its derivatives have been outlined in Fig. (**5**). Yue *et al.* (2016) reported synthesis of imidazole derivatives (route-a) using 2-hydroxy-1,2-diphenylethanone, 4-bromoaniline and ammonium acetate and aromatic aldehyde [43]. One-pot synthesis of imidazole derivative was reported *via* three component domino reaction of 2,2-dibromo-1,2-diarylethanones, ammonium acetate, and aryl aldehydes under catalyst-free conditions (route-b) [44]. Rajaraman *et al.* (2016) reported synthesis of imidazole derivatives (route-c) using mixture of benzil, ammonium acetate, furfurylamine and benzaldehyde in distilled ethanol in the presence of yttria as a catalyst [45]. Akbari *et al.* (2016) synthesized imidazole derivatives *via* reaction of benzil, benzaldehyde, benzylamine, and ammonium acetate under solvent free conditions (route-d) [46]. Synthesis of imidazole derivatives (route-e) was reported *via* (3+2) cycloaddition of imino carbenoids and nitriles [47]. Zheng *et al.* reported synthesis of imidazole derivatives *via* a three-component, one-pot

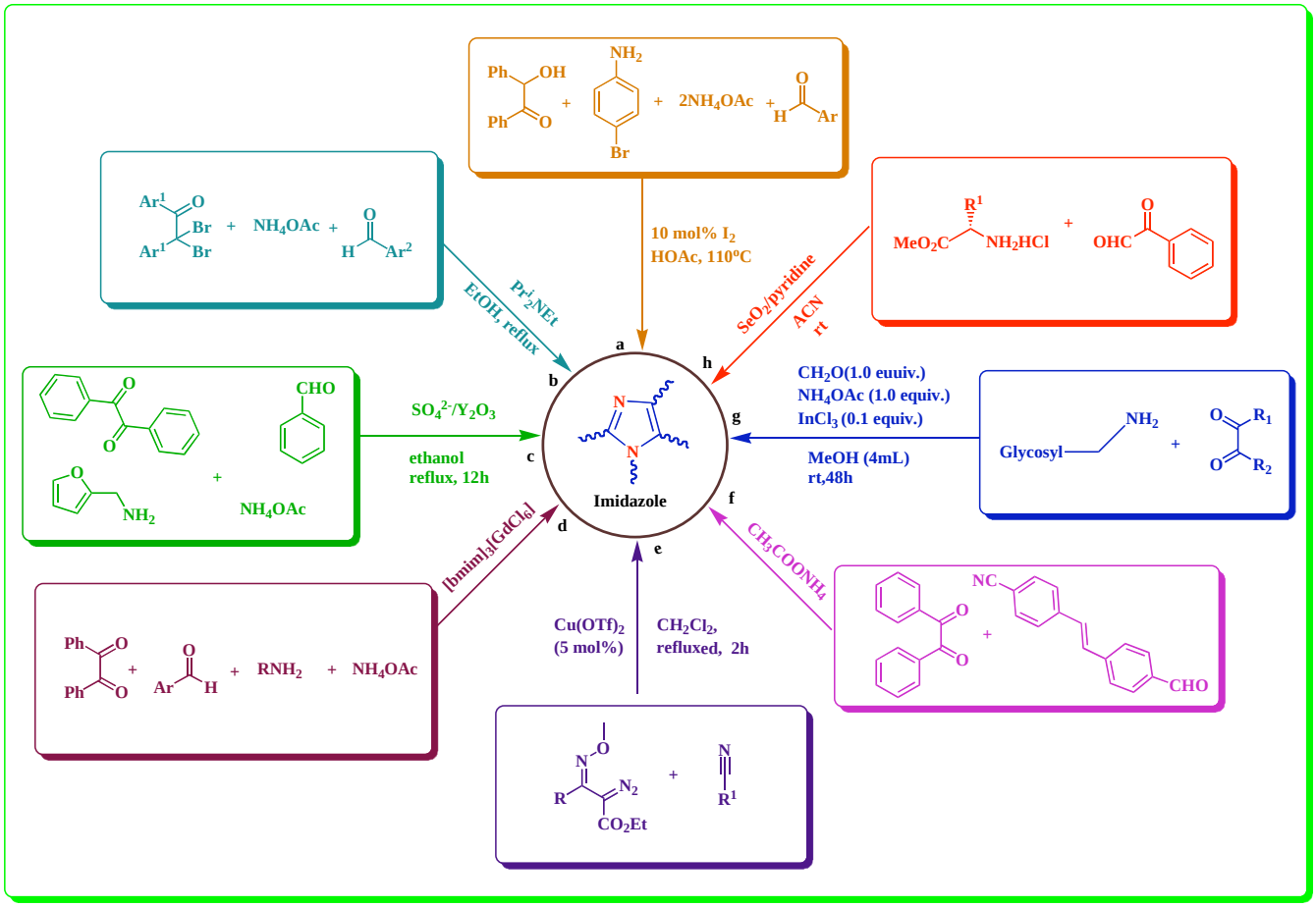


Fig. (5). Different routes for the synthesis of substituted diazoles (imidazoles). One pot multicomponent strategies have been used for the synthesis of various imidazole derivatives. In addition, ionic liquids were also explored as solvents cum catalysts for the synthesis of imidazoles.

reaction under solvent-free conditions (route-f) [48]. One-pot synthesis of imidazole derivatives was carried out using C-glycosylmethylamines, formaldehyde, ammonium acetate and benzil catalyzed by $InCl_3$ in methanol (route-g) [49]. Similarly, phenylglyoxal and glycine methyl ester hydrochloride were reacted in acetonitrile under basic conditions using selenium dioxide as catalyst for the construction of imidazole ring (route-h) [50].

4.3. Biological Activities

Diazoles have shown various biological activities such as antimicrobial, anti-inflammatory, analgesic, anti-tumor, anti-epileptic, antiviral, hypotensive, and anti-diabetic agents and anti-microbial activity. A large number of diazole containing drugs are used to treat various types of diseases. For example, zoledronicacid, azathioprine, and tipifarnib are used to treat cancer. Clotrimazole, miconazole, ketoconazole, and oxiconazole are used as antifungal agents. Metronidazole, benznidazole, ornidazole, and secnidazole are developed as antiparasitic agents. Cimetidine, imetit, immepip, and thioperamide are used as antihistaminic drugs. Nafimidone, fipamezole, and dexmedetomidine are antineuropathic. Losartan, eprosartan and olmesartan are antihypertensive drugs (Table **2**).

Table 2. Drugs in clinical practice containing a diazole nucleus.

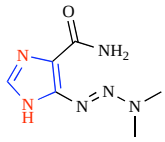
Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
ANTICANCER	Dacarbazine	 5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide	Non-cell cycle specific, alkylates DNA and RNA, causes DNA double strand breaks and apoptosis	Malignant melanoma, Hodgkin's disease, skin cancer lymphomas, sarcoma	[51-54]

Table 2. contd….

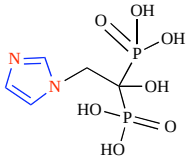
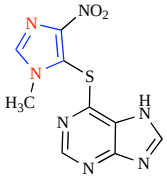
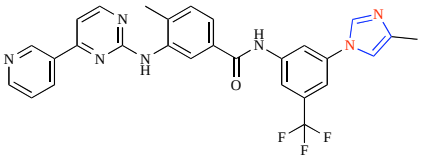
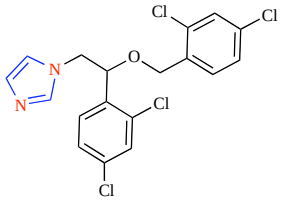
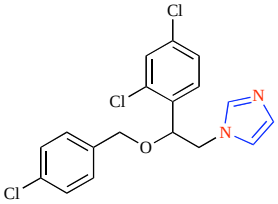
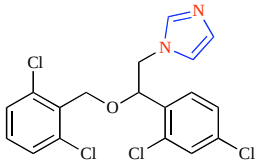
Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
	Zoledronic Acid	 [1-hydroxy-2-(1H-imidazol-1-yl)ethane-1,1-diyl]bis(phosphonic acid)	Inhibits bone resorption *via* actions on osteoclast activity, leading to indirect increase in bone density	Skeletal diseases	[55-57]
	Azathioprine	 6-[(1-methyl-4-nitro-1H-imidazol-5-yl)thio]-7H-purine	Purine antimetabolite, converted to 6-MP, inhibit synthesis DNA, RNA and proteins, interferes with cellular metabolism, inhibit mitosis	Organ transplantation, rheumatoid arthritis, Crohn's disease and polymyosites	[58-61]
	Nilotinib	 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)- 5-(trifluoromethyl)phenyl]-3- [(4-pyridin-3-ylpyrimidin-2-yl) amino]benzamide	Selectively binds with high affinity to ATP-binding site of BCR-ABL kinase inhibiting cell proliferation in cell lines and in primary Ph^+ CML leukemia cells. Active against imatinib-resistant froms of Bcr-Abl Inhibits PDGFR and c-kit kinase	Blood cancer, chronic myelogenous leukemia-CML	[62-66]
ANTIFUN-GAL	Miconazole	 (RS)-1-(2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole	Inhibits the synthesis of ergosterol	Athlete's foot, Ring-worm and jock itch	[67-70]
	Econazole	 (RS)-1-{2-[(4-Chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole	Inhibits the synthesis of ergosterol	Athlete's foot, ring-worm, pityriasis versi-color and jock itch	[71, 72]
	Isoconazole	 (RS)-1-[2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole	Inhibits the synthesis of ergosterol	Vaginal and fungal skin infections	[73, 74]

Table 2. contd….

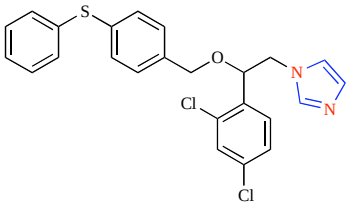
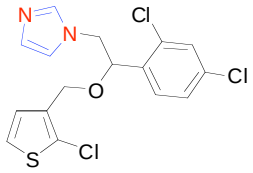
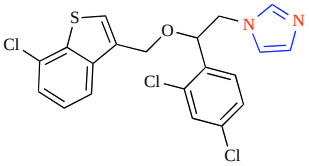
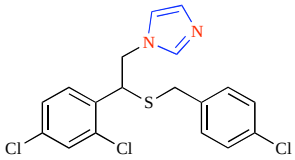
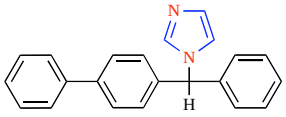
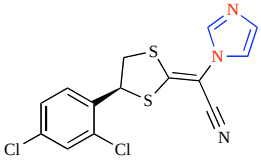
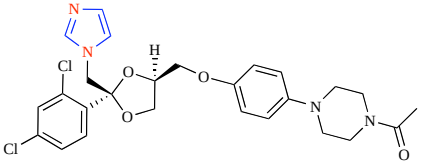
Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
	Fenticonazole	 1-[2-(2,4-dichlorophenyl)-2-{[4-(phenylsulfanyl)phenyl]methoxy}ethyl]-1H-imidazole	Inhibits the synthesis of ergosterol	Vaginal fungal infections	[75]
	Tioconazole	 (RS)-1-[2-[(2-Chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole	Inhibits the synthesis of ergosterol	Vulvovaginal candidiasis, Vaginal yeast infections	[76-78]
	Sertaconazole	 1-{2-[(7-Chloro-1-benzothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole	Inhibits the synthesis of ergosterol	Skin infections such as athlete's foot	[79-81]
	Sulconazole	 1-(2-{[(4-Chlorophenyl)methyl]sulfanyl}-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole	Inhibits the synthesis of ergosterol	Skin infections such as athlete's foot, ringworm, jock itch and sun fungus	[82, 83]
	Bifonazole	 (RS)-1-[Phenyl(4-phenylphenyl)methyl]-1H-imidazole	Inhibits the synthesis of ergosterol	Skin fungal infections	[84-86]
	Luliconazole	 (2E)-[(4R)-4-(2,4-Dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazol-1-yl)acetonitrile	Inhibits the synthesis of ergosterol	Skin infections such as athlete's foot, ringworm, jock itch	[87, 88]
	Ketoconazole	 1-[4-(4-{[(2R,4S)-2-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]ethan-1-one	Inhibits the synthesis of ergosterol	Fungal infections	[89, 90]

Table 2. contd….

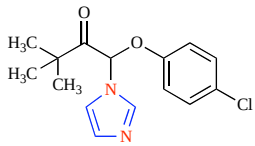
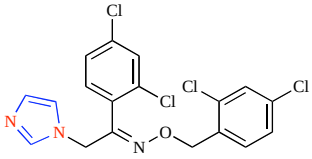
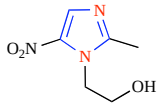
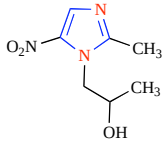
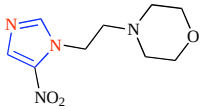
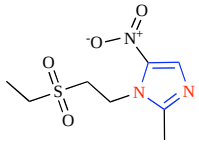
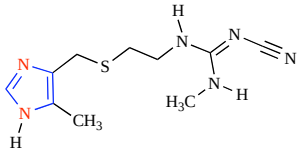
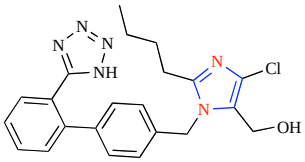
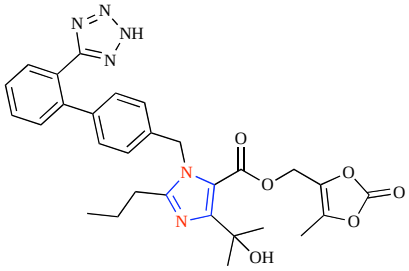
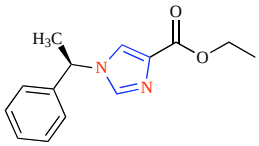
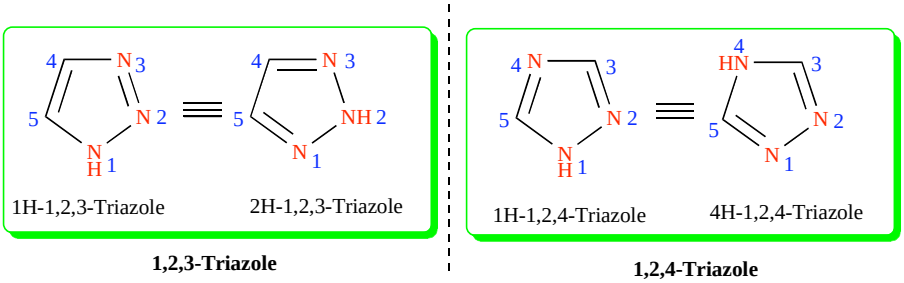
Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
	Climbazole	 (RS)-1-(4-Chlorophenoxy)-1-imidazol-1-yl-3,3-dimethylbutan-2-one	Inhibiting microbe growth	Skin infections such as dandruff and eczema	[91-93]
	Oxiconazole	 (E)-[1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethylidene][(2,4-dichlorophenyl)methoxy]amine	Inhibits the synthesis of ergosterol	Skin infections such as athlete's foot, jock itch and ringworm	[94, 95]
ANTIBAC-TERIAL	Metronidazole	 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol	Inhibit nucleic acid synthesis	Trichomonas, vincent's organisms, anaerobic bacteria, giardias and amebiasis	[96-99]
	Secnidazole	 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)propan-2-ol	Inhibit nucleic acid synthesis	Giardiasis, amebiasis and bacterial vaginosis	[100-103]
	Nimorazole	 4-[2-(5-nitro-1H-imidazol-1-yl)ethyl]morpholine	Inhibit nucleic acid synthesis	Infection such as amebi-asis, trichomoniasis and treatment of Head and Neck cancer	104-106]
	Tinidazole	 1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole	Inhibit nucleic acid synthesis	Amebiasis, giardiasis human trichomoniasis and bacterial vaginosis	[107-110]
ANTIHIS-TAMINIC	Cimetidine	 (E)-2-cyano-1-methyl-3-(2-(((5-methyl-1H-imidazol-4-yl)methyl)thio)ethyl)guanidine	Blocks H2- receptors of gastric parietal cells, Inhi-bition of gastric acid secre-tions	Heartburn and peptic ulcers	[111-113]
ANTIHYPER TENSIVE	Losartan	 (2-butyl-4-chloro-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazol-5-yl)methanol	Blocking of angiotensin II receptors	High blood pressure	[114-118]

Table 2. contd….

Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
	Olmesartan	 (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-imidazole-5-carboxylate	Blocking of angiotensin II receptor	High blood pressure	[119-121]
GENERAL ANAES-THETICS	Etomidate	 ethyl 3-[(1R)-1-phenylethyl]imidazole-5-carboxylate	Block 11-β hydroxylase	Conscious sedation	[122-124]

5. TRIAZOLE

There are two isomers of triazole; 1,2,3-triazole and 1,2,4-triazole depending upon the relative positions of the nitrogen atoms in the ring [125, 126].



5.1. 1,2,3-triazoles

The structural isomers of the 1,2,3-triazole exhibit tautomerism and exist in two tautomeric forms. For example, 1,2,3-triazoles can exists as 1,2,3-(1*H*) triazole and 1,2,3-(2*H*) triazole.

5.1.1. Synthetic Strategies

The synthetic strategies for the construction of triazole ring have been depicted in the Fig. (**6**). Xavier *et al.* reported synthesis of novel N-aryl-1,2,3-triazoyl carboxamides from β-oxo-amides and substituted aryl azides (route-a) [127]. An azide derivative was reacted with phenylacetylene in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in t-butanol and water (1:1, v/v) for the formation of triazole derivatives (route-b) [128]. In 2016, synthesis of 1,2,3-triazole derivative was reported from ethyl acetoacetate, NH_2NH-Boc, and imidazole sulfonyl azide in the presence of DBU in CH_3CN/Toluene (1:1) as solvent (route-c) [129]. Synthesis of triazole-O-glycoconjugate derivatives was achieved by consecutive glycosylation and cycloaddition reaction in one-pot (route-d) [130]. Narsimha *et al.* reported synthesis of triazole derivatives from prop-2-yn-1-yl-1*H*-indole-2-carboxylate and phenyl azides in the presence of cuprous iodide (CuI) as a catalyst in THF at room temperature (route-e) [131]. Gonzalez-Calderon *et al.* disclosed the synthesis of 1,5-disubstituted 1,2,3-triazoles from azides by coupling them with β-ketophosphonates (route-f) [67]. Gangaprasad *et al.* reported synthesis of 1,2,3-triazoles by [3+2] cycloadditions of organic azides with nitroolefins in the presence of CuO catalysed nanoparticles under solvent-free conditions (route-g) [132]. One-pot synthesis of 1,4-disubtituted 1,2,3-triazoles was reported using copper nano particles at room temperature. Copper nanoparticles were synthesized using green biosynthetic method by reduction of $CuCl_2{\cdot}2H_2O$ solution with aqueous extract of leaves of *Otostegia persica*. This extract contained flavonoid and other phenolics as main components which act as reducing agents and efficient stabilizer (route-h) [133].

5.2. 1, 2, 4-triazoles

In 1, 2, 4-triazoles, nitrogen atoms are present at 1, 2 and 4 positions of the pentacyclic ring. 1, 2, 4-triazoles exist in two tautomeric forms; 1,2,4(1*H*) triazole and 1,2,4(4*H*) triazole.

5.2.1. Synthetic Strategies

The synthetic strategies have been outlined for the synthesis of 1,2,4-triazole in Fig. (**7**). In 2016, one-pot synthesis of 3,5-disubstituted-1*H*-1,2,4-triazole derivatives was reported using I_2/Cs_2CO_3 as catalyst and base respectively. The reaction involves one-pot sequential C–N and N–N bond forming reactions (route-a)

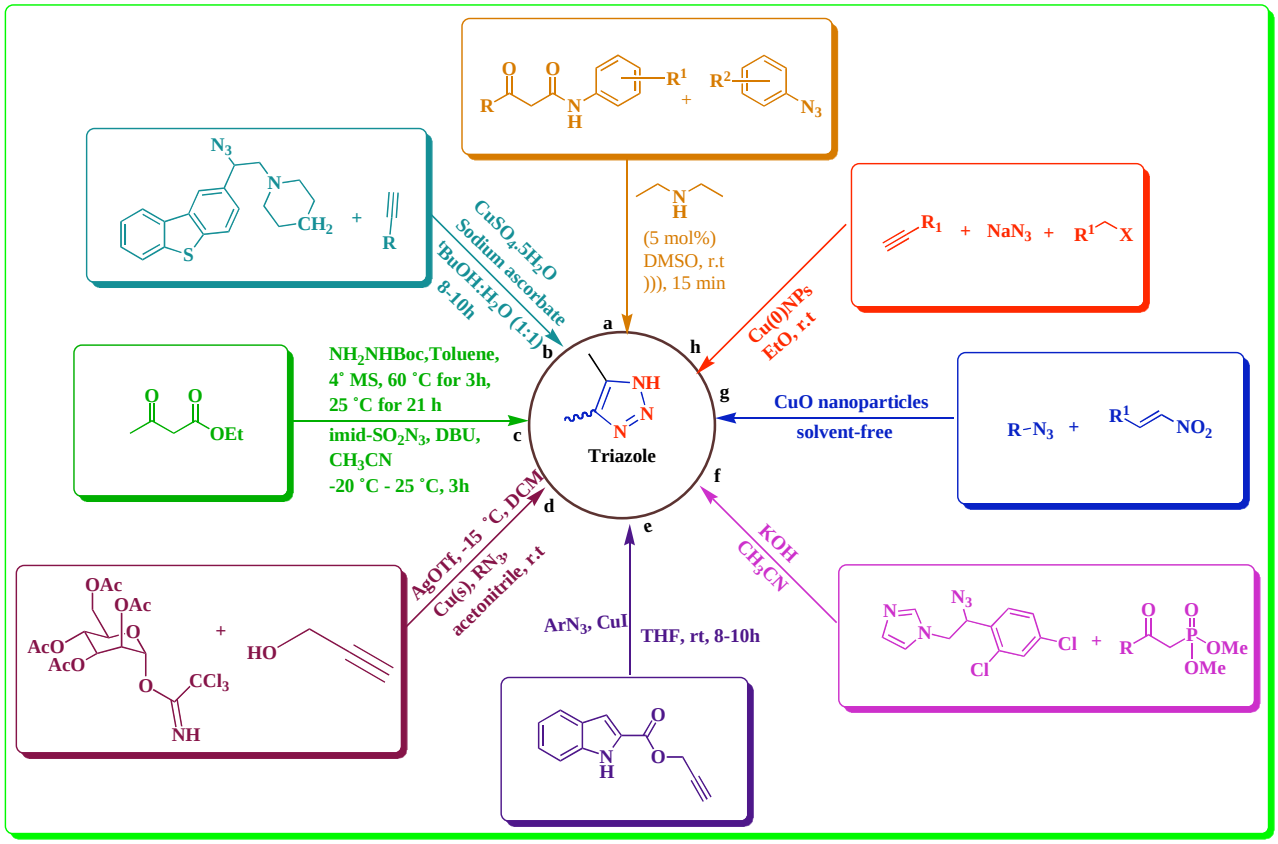


Fig. (6). Different routes for the synthesis of substituted 1,2,3-triazoles.

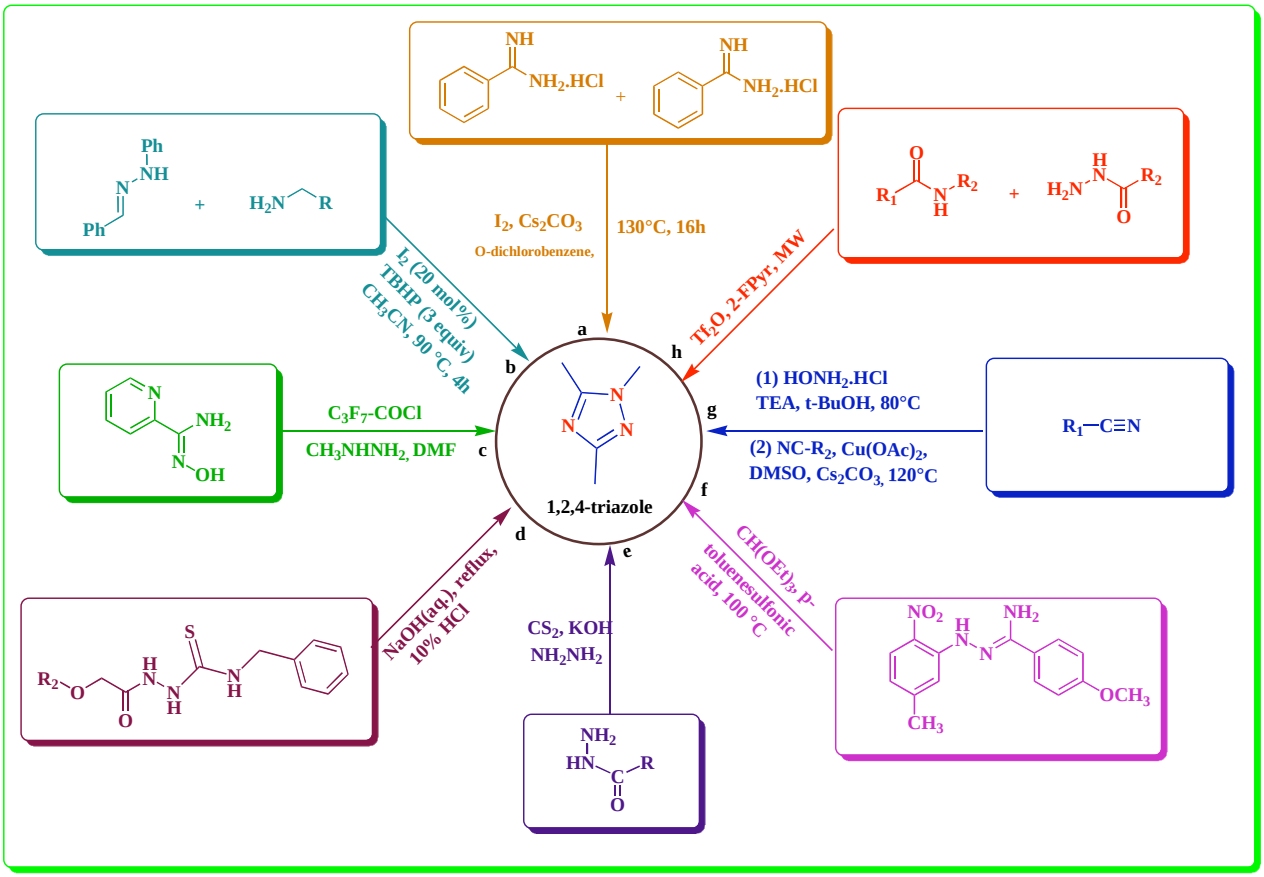


Fig. (7). Different routes for the synthesis of substituted 1,2,4-triazoles.

Table 3. Drugs in clinical practice containing a triazole nucleus.

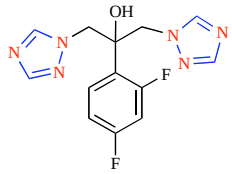
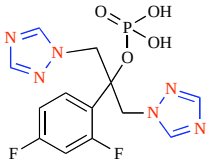
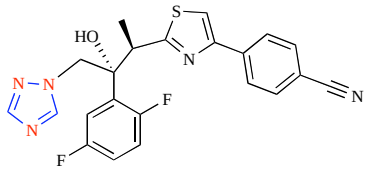
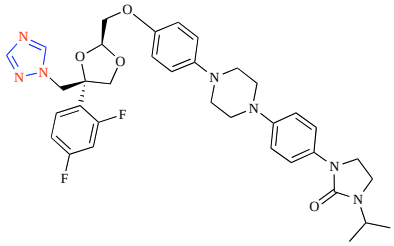
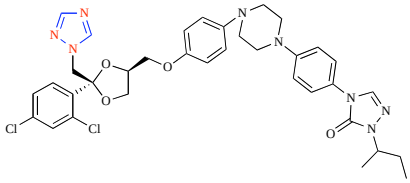
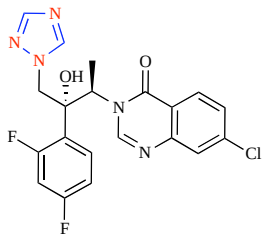
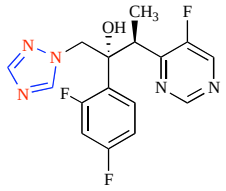
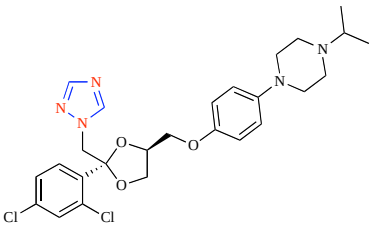
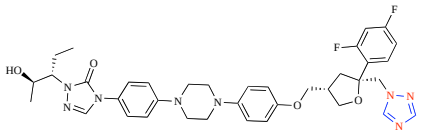
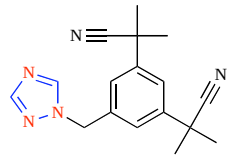
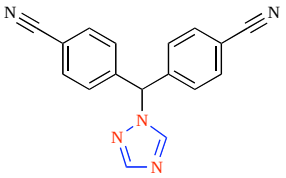
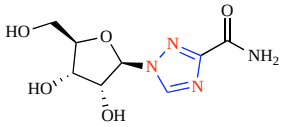
Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
ANTIFUNGAL	Fluconazole	 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol	14-alpha demethylase inhibitors	Systemic fungal infections	[142-144]
	Fosfluconazole	 {[2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-yl]oxy}phosphonic acid	14-alpha demethylase inhibitors	Systemic fungal infections	[145, 146]
	Isavuconazole	 4-(2-((2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)butan-2-yl)thiazol-4-yl)benzonitrile	Ergosterol biosynthesis	Invasive fungal Infections	[147-149]
	Pramiconazole	 1-[4-[4-[4-[[(2S,4R)-4-(2,4-Difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone	Ergosterol biosynthesis	Acute skin and fungal infections	[150, 151]
	Itraconazole	 4-(4-(4-(((2R,4S)-2-((1H-1,2,4-triazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl)-1-(sec-butyl)-1H-1,2,4-triazol-5(4H)-one	Ergosterol biosynthesis	Fungal infections	[152-154]
	Albaconazole	 7-Chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one	Ergosterol biosynthesis	Fungal infections	[149, 155]

Table 3.contd…

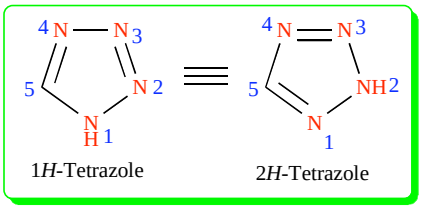
Activity	Name	Structure And Chemical Name	Mechanism of Action	Use	Reference
	Voriconazole	 (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol	Ergosterol biosynthesis	Fungal infections	[156-158]
	Terconazole	 1-(4-(((2R,4S)-2-((1H-1,2,4-triazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-4-isopropylpiperazine	Ergosterol biosynthesis	Vaginal fungal infection	[159-162]
	Posaconazole	 4-(4-(4-(4-(((3S,5S)-5-((1H-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)tetrahydrofuran-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2R,3S)-2-hydroxypentan-3-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one	Ergosterol biosynthesis	Invasive fungal infections	[163-166]
NON STER-OIDAL ARO-MATASE INHIBITORS	Anastrozole	 2,2'-(5-((1H-1,2,4-triazol-1-yl)methyl)-1,3-phenylene)bis(2-methylpropanenitrile)	Block conversion of androstenedi-one to estrone	Breast cancer	[167-170]
	Letrozole	 4,4'-((1H-1,2,4-triazol-1-yl)methylene)dibenzonitrile	Blocks conversion of androstenedi-one to estrone	Breast cancer	[171-174]
ANTIVIRAL	Ribavirin	 1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1H-1,2,4-triazole-3-carboxamide	Inhibition of viral protein synthesis	Hepatitis C infec-tion	[175, 176]

[134]. Synthesis of 1,2,4-triazoles from hydrazones and aliphatic amines has been reported under aerobic oxidative conditions. The reaction proceeds through a cascade C−H functionalization, double C−N bond formation, and oxidative aromatization (route-b) [135]. Similarly, N-hydroxypicolinamidine is reacted with fluorinated acyl chloride and methyl hydrazine in the presence of DMF to obtain corresponding 1,2,4-triazoles (route-c) [136]. Kulabas *et al.* disclosed cyclo condensation of thiosemicarbazides using sodium hydroxide under reflux conditions leading to the formation of 5-(aryloxymethyl)-4-benzyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (route-d) [137]. Asif *et al.* reported synthesis of 1,2,4-triazole derivatives using hydrazides, and carbon disulfide in the presence of potassium hydroxide (route-e) [138]. Catarzi *et al.* disclosed the synthesis of 1,2,4-triazole derivatives through cyclization of corresponding amidrazone in the presence of $CH(OEt)_3$ using *p*-toluenesulfonic acid (route-f) [139]. In 2015, Xu *et al.* reported one-pot synthesis of 1,2,4-triazoles from nitriles and hydroxylamine in the presence of copper-catalyst (route-g) [140]. The reaction proceeds *via* sequential intramolecular addition of hydroxylamine to nitrile, leading to the formation of aldoxime followed by reaction

with another nitrile. Bechara *et al*. reported synthesis of 3,4,5-trisubstituted triazoles derivative from secondary amides and acyl-hydrazides. The reaction proceeds *via* triflic anhydride mediated activation followed by microwave-induced cyclodehydration (route-h) [141] (Table **3**).

6. TETRAZOLE

Tetrazoles are not found in nature and have been prepared synthetically. Tetrazoles exist in two tuatomeric forms viz 1*H*-tetrazole and 2*H*-tetrazole. After an accidental discovery of tetrazole in 1885, development of various new strategies and their application remained a topic of interest for the organic and medicinal chemists. In medicinal chemistry, tetrazoles are used as lipophilic spacers considered stable (from the viewpoint of metabolism) surrogate for carboxylic acid group [177]. In addition, tetrazoles are also used as specialty explosive and as ligand in coordination chemistry. Moreover, various tetrazole derivatives are important precursors for the synthesis of complex heterocyclic compounds hitherto difficult to prepare.



6.1. Synthetic Strategies

Various strategies for the synthesis of tetrazole are depicted in Fig. (**8**). Hameed *et al.* reported one-pot multicomponent reaction between acetophenone, malononitrile and trimethylsilyl azide ($TMSN_3$) in the presence of TBAF to afford tetrazole (route-a) [178]. In 2016, an efficient and economical synthesis of 5-substituted-1*H*-tetrazoles was achieved through Pb(II) salt catalysed [3+2] cycloaddition reaction of nitriles and sodium azide (route-b) [179]. Similarly, Cu-MCM-41 was used as an efficient catalyst for the synthesis of 5-substituted-1*H*-tetrazoles *via* [3+2] cycloaddition reaction of nitriles and sodium azide (route-c) [180]. Synthesis of 2-aryl-2*H*-tetrazoles was reported *via* a regioselective [3+2] cycloaddition reaction (route-d) [181]. One-pot synthesis of tetrazole was accomplished using aldehydes, sodium azide and N-hydroxyl amine (route-e) [182]. A novel and efficient synthesis of 1*H*-tetrazolystilbenes was achieved using tributyltin azide and cyanostilbenes (route-f) [183]. One-pot synthesis of tetrazole derivatives was achieved *via* tandem dipolar cycloaddition reaction (route-g), which was further used for Knoevenagel condensation reaction [184]. Synthesis of tetrazole derivatives was reported using *N*-benzyloxycarbonyl (Cbz)-L-alanine, benzylamine and trimethylsilylazide in the presence of $POCl_3$ in CH_3CN (route-h) [185] (Table **4**).

CONCLUSION

Heterocyclic ring containing a nitrogen atom are essential part of many agrochemicals and drugs molecules. Nitrogen containing heterocyclic ring can act as a pharmacophore in the drug molecule and possesses hydrogen bond accepter and hydrogen bond donor capabilities at the receptor site. In addition, *N*-heterocyclic rings can exhibit polar interactions at the target site. The presence of *N*-heterocyclic rings can influence the pharmacokinetics, pharmacodynamics, pKa and bioavailability profile of the drug molecules. Compounds containing monocyclic azole rings showed various biological activities and number of molecules are in clinical practice. Many drugs especially antibiotics are becoming obsolete due to the development of multidrug resistance. Moreover, toxicity and other side effects of some drugs necessitated the quest for safer and more potent drug candidates. A number of important leads and

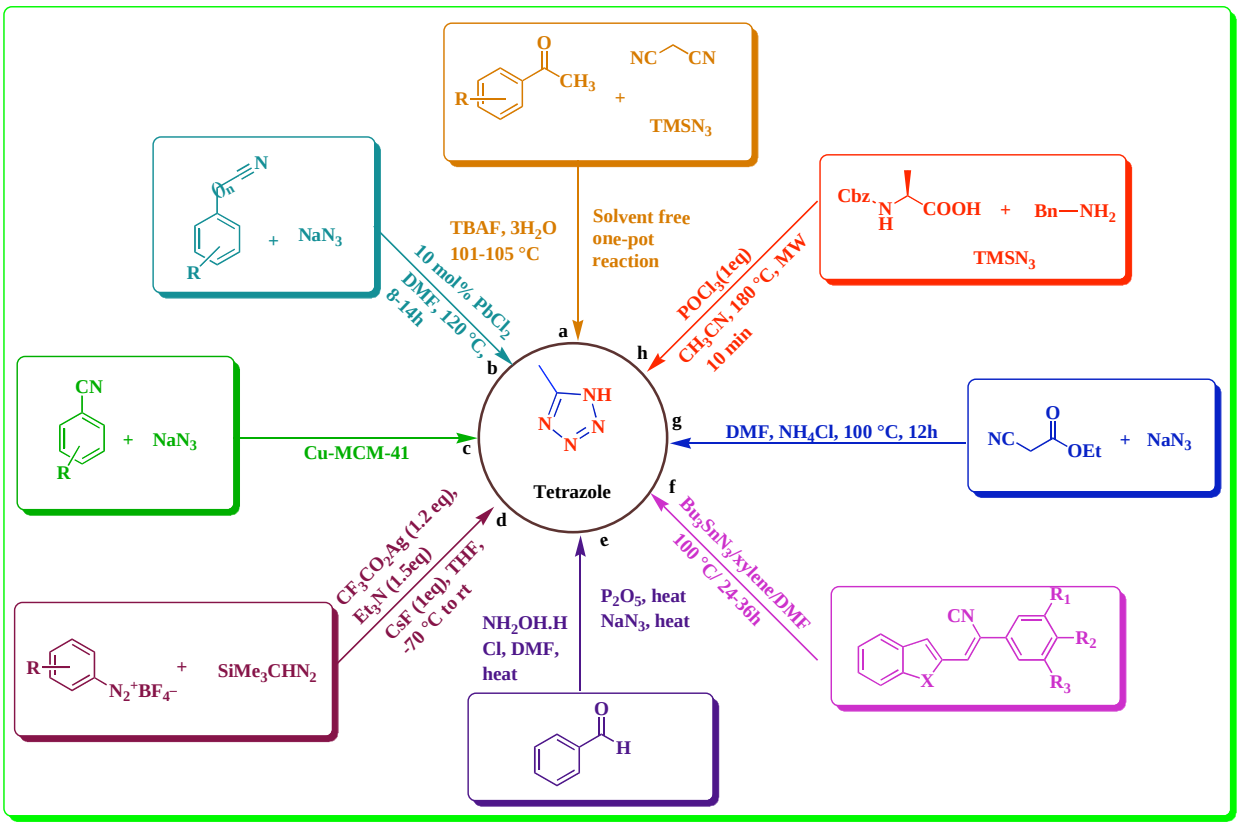
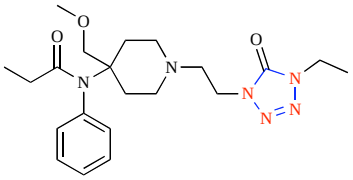
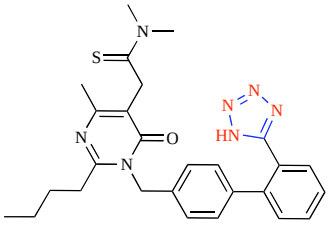
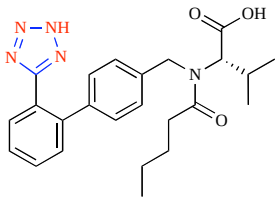
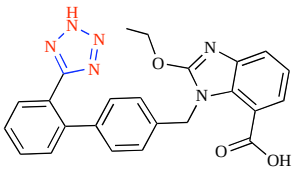
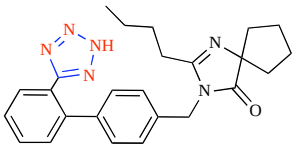


Fig. (8). Different routes for the synthesis of substituted tetrazoles. Most of the synthetic routes make use of different salts of azide.

Table 4. Drugs in clinical practice containing a tetrazole nucleus.

Activity	Name	Structure and Chemical Name	Mechanism of Action	Use	Reference
OPIOID ANALGE-SICS	Alfentanil	 N-(1-(2-(4-ethyl-5-oxo-4,5-dihydro-1H-tetrazol-1-yl)ethyl)-4-(2-oxopropyl)piperidin-4-yl)-N-phenylpropionamide	Narcotic agonist analgesic, increase pain threshold, inhibits ascending pain pathways, alters pain perception	Anaesthesia in surgery	[186]
ANTIHYPE RTENSIVE	Fimasartan	 2-(2-Butyl-4-methyl-6-oxo-1-{[2'-(1H-tetrazol-5-yl)-4-biphenylyl]methyl}-1,6-dihydro-5-p1yrimidinyl)-N,N-dimethylethanethioamide	Angiotensin type 1 receptor antagonists	Hypertension and Heart failure	[187-189]
	Valsartan	 (S)-3-methyl-2-(N-{[2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido)butanoic acid	Angiotensin II receptor blocker (ARB), inhibits vasoconstriction and aldosterone secreting effects of angiotensin II	High blood pressure, Congestive, Heart failure	[190-192]
	Candesartan	 2-ethoxy-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-1,3-benzodiazole-7-carboxylic acid	Angiotensin II receptor blocker (ARB), inhibits vasoconstriction and aldosterone secreting effects of angiotensin II	Hypertension	[193-195]
	Irbesartan	 2-butyl-3-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1,3-diazaspiro[4.4]non-1-en-4-one	Angiotensin II receptor blocker, inhibits vasoconstrictior and aldosterone secreting effects of angiotensin II	Hypertension	[196-200]

potential drug candidates containing azole nucleus are in various stages of clinical developments. Thus, simple, atom economic and more efficient synthetic strategies are desired for the synthesis of new libraries of the compounds. These novel molecules may be developed as drug candidates for the treatment of number of complicated diseases. Various monocyclic azoles and their biological activities.

LIST OF ABBREVIATIONS

AcOH	=	Acetic acid
CUI	=	Cuprous iodide
CUO	=	Cupric Oxide
DBU	=	1,8-Diazabicyclo [5.4.0] undec-7-ene
DNA	=	Deoxyribonucleic acid
DMF	=	Dimethyl Formamide
DMSO	=	Dimethyl Sulfoxide
P-TsOH	=	ρ-Toluenesulfonic acid
RNA	=	Ribonucleic acid
SSC	=	Silica Sodium Carbonate
TBAF	=	Tetrabutyl ammonium fluoride
THF	=	Tetrahydrofuran

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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