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Review

MICROWAVE-ASSISTED SYNTHETIC APPROACHES TO BIOLOGICALLY ACTIVE N-BASED FIVE-MEMBERED HETEROCYCLES AS RESPONSE TO GREEN CHEMISTRY

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The broad pharmacological effects of 5-membered nitrogen containing heterocycles require rapid and environmental friendly methods for their synthesis. Microwave irradiation has been heavily applied in the field of organic synthesis since its introduction. The beneficial reduction of reaction time from hours or even days to minutes is one of many advantages of MW assisted synthesis compared to conventional methods. Additionally, achieving energy efficiency protocols, higher yields, selective heating and easy manipulation of the reaction have further established the MW assisted organic synthesis as a potential replacement of conventional syntheses. This review focuses on recently reported papers in the field of microwave-assisted synthesis of 5-membered heterocycles containing nitrogen atom, including pyrroles, pyrazoles, imidazoles, triazoles and tetrazoles. After each reported case a modest synthetic scheme is provided.

INTRODUCTION

The term "Green chemistry" was first introduced in early 1990s and described by Anastas and Warner later in 1998, when they discussed the twelve principles which constructed the base of Green chemistry **(Figure 1)**.[1,2] The major aim of the green protocols is the implementation of sustainable processes, which lower the environmental damage. Moreover nowadays, the need of cleaner reactions is rapidly growing due to the increasing environmental pollutions.[3] Nevertheless, toxic solvents are frequently used in organic syntheses using conventional heating.[4] Polluting the environment when volatile solutions are present have been reported in numerous papers.[5] The ideal conditions proposed by the principles of Green chemistry are the removal of hazardous solvents or replacing them with water. Furthermore, the liquids should be inexpensive and maintained throughout the synthetic process.[6]

Microwave chemistry is the science of utilizing microwave irradiation to synthetic reactions. The former represents a major breakthrough in the methodology of the synthetic chemistry, since MW provides alternative method for heating. There are numerous papers that have applied the MW irradiation in organic reactions and large number of them have eliminated the need of solvents.[7] Utilizing solvent-less reactions when using MW reactor, fulfill principle 5 of the green protocol. Furthermore, the synthetic protocols which utilize the MW irradiation as a heating source are highly efficient in terms of energy consumption.[8] The latter observation further underlines the "Green" effect of the MW ovens.

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Fig. 1 – The principles of green chemistry.

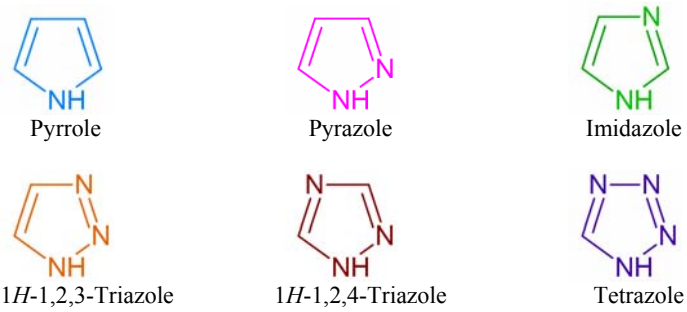


Fig. 2 – Structures of five-membered heterocycles containing nitrogen atom.

Heterocyclic compounds play an important role in our lives. They have been found in numerous key biomolecules like enzymes, vitamins, natural products. Wide variety of active molecules contain five-membered heterocyclic moiety with nitrogen atom (**Figure 2**) in their structures. Such drugs with antifungal, anticancer, antidiabetic, anti-hypertensive, anti-inflammatory, antiviral, anti-convulsant, antibacterial, antidepressant properties have been reported.[9,10] Examples of commercial drugs that contain five-membered ring with nitrogen atom are also available including atorvastatin, tolmetin, indomethacin, miconazole, ketoconazole, clotrimazole, zolpidem, sildenafil and many others.[11-13] However, the conventional synthesis of these drugs requires long reaction times and in some cases hazardous solvents. Microwave irradiation successfully deals with these problems as discussed in several papers.[14-16]

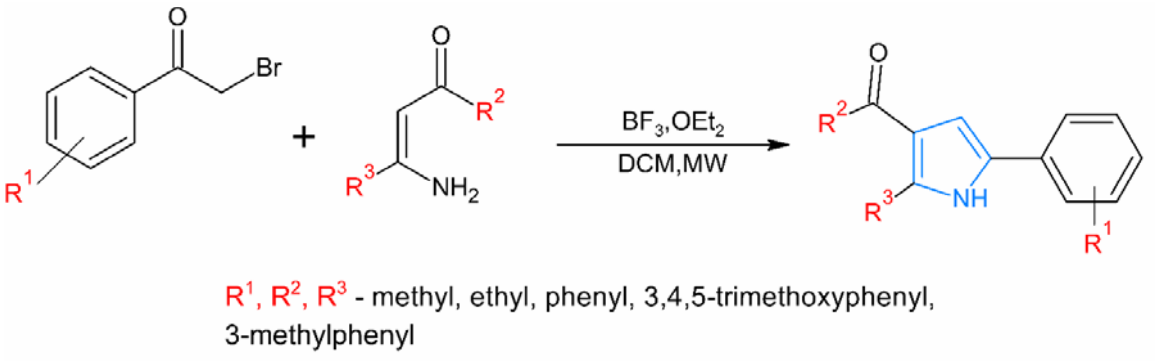
The first implementation of MW irradiation for synthetic purposes was documented in 1986 by Gedye *et al.*[17] They carried out 4 reactions in a MW oven and noticed considerable reduction of the reaction time. Ever since MW assisted organic synthesis is rapidly growing as a synthetic technique based on the increasing number of published papers in that field.[18] As reviewed above, one of the main advantages of MW heating is the expeditious reaction time compared to conventional heating.[19] Moreover, higher yields, highly reproducible results, higher purity and decrease of energy used have been reported.[20] Recent work has shown a significant reduction of the activation energy when MW heating had been applied.[21] The paper suggested that the changes of the molecular rotations promote decrease of the Ea.

In the present review we tried to demonstrate the significant role of microwave irradiation in the synthesis of five membered *N*-containing heterocycles and their application in medicine.

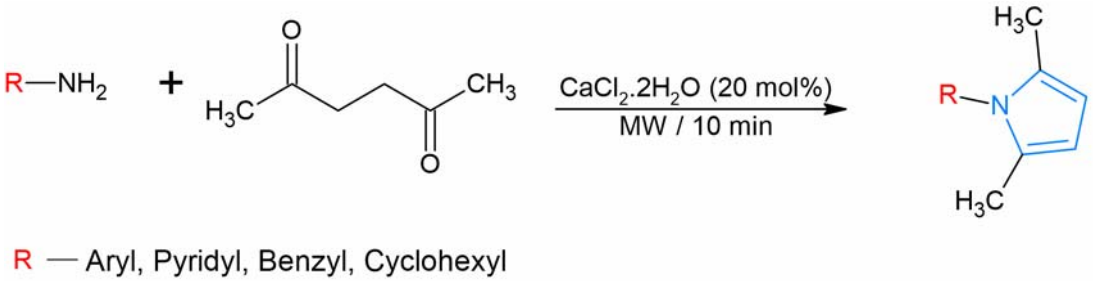
1. Pyrrole

There are many approaches for synthesis of pyrrole, some of which include the Knorr, Pall – Knorr, Hantzsch condensation and Clauson – Kaas

reactions, which require conventional heating and a long reaction time.[11] In recent years, the use of microwave irradiation has been observed, which significantly improves pyrrole synthesis. Reddy *et al.* described the synthesis of pyrrole derivatives in high yields from aliphatic amino unsaturated ketone derivatives in short reaction times after applying microwave irradiation (**Scheme 1**).[20] The reported yields were in the range of 68-93%, with only two compound demonstrating yields below 80%. Furthermore, the authors have described the effects of different solvents and catalysts, which have further optimized the reaction yield and speed. In the final phase of the study, a proposed reaction mechanism has been suggested.



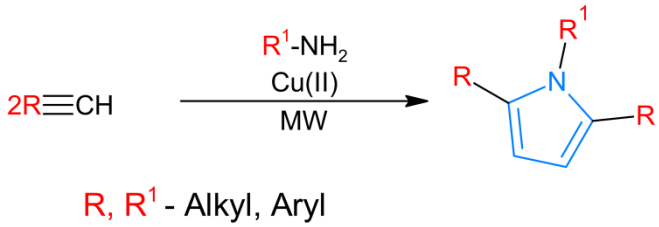
Scheme 1 – Synthesis of trisubstituted pyrroles from aliphatic amino unsaturated ketone derivatives.



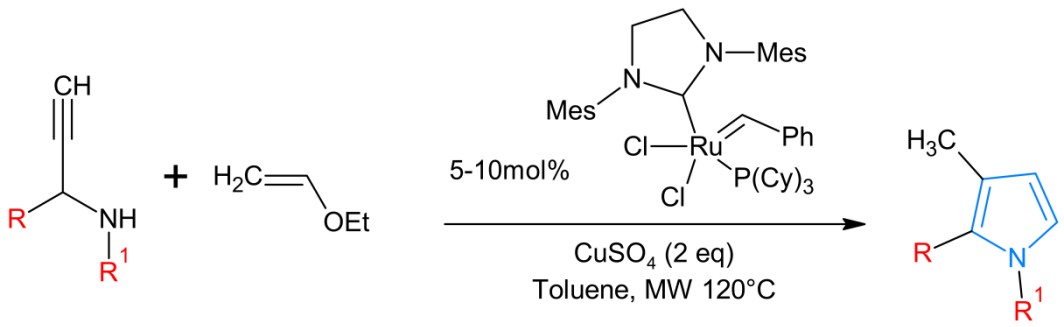
Scheme 2 – Synthesis of substituted pyrroles from hexane-2,5-dione with primary aromatic and aliphatic amines.

The utilization of MW synthesis as a green friendly method for the synthesis of pyrroles has been noted by Aghapoor *et. al* (**Scheme 2**). The work has demonstrated a rapid, high in yield and clean reaction protocol by applying MW irradiation and low-cost and nontoxic catalyst. The optimal catalyst has been found to be a calcium (II) chloride out of six different alkali and alkali-earth catalysts. Moreover, the reaction was carried solvent free.[22]

A recent paper published by Lee *et al.* displayed a MW irradiated synthesis of substituted pyrroles from 1-alkynes and primary amines (**Scheme 3**).[23] Initially, the synthetic protocol was built and optimized for the production of furans. However, the authors obtained 1,2,5- trisubstituted pyrroles with traces of furan products, when an amine was implanted in the reaction. The small amounts of furan side products were discussed to be result from the acetate ion in $Cu(OAc)_2 \cdot H_2O$. Reaction time of 10 min. and heating up to 150°C were utilized. The yields varied from 42 to 82%. A possible mechanism has been also provided.

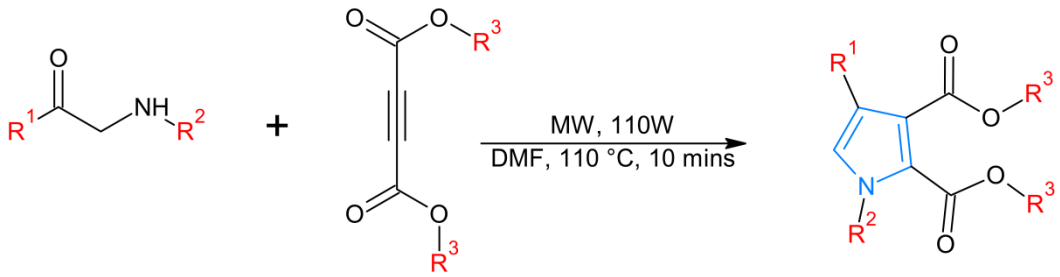


Scheme 3 – Microwave irradiation synthesis of 2,5-disubstituted pyrroles using a Cu(II)-catalyst.



R, R^1 - Ar, Alk, Het, Ac, Ts, Boc and Ph

Scheme 4 – Synthesis of 1,2,3-substituted pyrroles from propargylamines with ethyl vinyl ether.



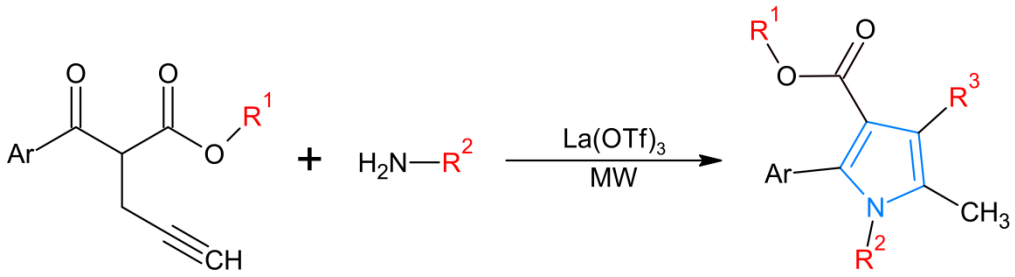
R^1, R^2, R^3 - Ethyl, methyl, methoxy, naphtyl, chloride, bromide

Scheme 5 – Synthesis of tetrasubstituted pyrrole analogues from dialkyl acetylenedicarboxylates with substituted monophenacylanilines.

A facile, one pot, MW-assisted synthesis of 1,2,3-substituted pyrroles has been proposed by Chachignon *et al*. (**Scheme 4**).[24] The paper has discussed a major optimization of the reaction protocol after altering solvents, catalysts, catalysts concentrations, reaction times and temperatures. The utilization of ethyl-vinyl ether, toluene, 2 eq. of copper (II) sulfate and Grubbs'catalyst were found to be the optimal reaction conditions. Only when two phenyl moieties were included as substituents, the protocol failed to produce the desired products. Overall, discussed method provides versatile and rapid approach for the MW synthesis of 1,2,3-substituted pyrroles.

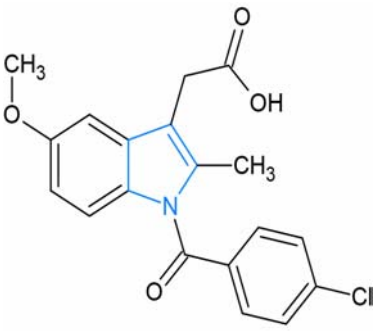
An efficient, catalyst-free microwave synthesis of tetrasubstituted pyrroles has been recently published (**Scheme 5**).[25] The authors reacted α-amino ketones with dialkyl acetylene dicarboxylates in order to obtain dialkyl 1,4-diaryl-pyrrole-2,3-dicarboxylates. The effects of MW power, temperate and the solvent has been also evaluated. The reaction times have not exceeded 10 min, in all cases, however, no standard solvent was found. The yields were ranging from 37 to 80%. In addition to the synthetic part of the work, the authors also discussed the presence of axial chirality in one of the products, which was not found in the rest of the structures.

Tan *et al*. have developed a Lewis acid catalyzed microwave irradiation synthesis of various α-aryl tetrasubstituted pyrroles through condensation/alkyne azacyclization/ isomerization sequence in acceptable to good yields (**Scheme 6**).[26] After several optimizations, the authors have underlined that the optimal Lewis acid was $La(OTf)_3$ with $PhCF_3$ as a solvent. In the observed cases, copper salts demonstrated poor results. Furthermore, two equivalents of the amine substrates have provided the best yield with temperatures over 120°C. Overall, the discussed reaction gave a suitable MW synthetic protocol for the synthesis of substituted pyrroles applying wide range of substrates – 4-methoxybenzylamine, 2-furylmethylamine, tryptamine, isobutylamine, methoxyethylamine, 4-morpholinepropylamine, cyclopropylamine, *p*-anisidine.

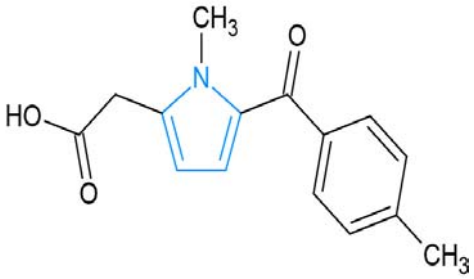


R^1, R^2, R^3 - Aliphatic amines, Ethyl, P-methoxybenzyl, Hydrogen

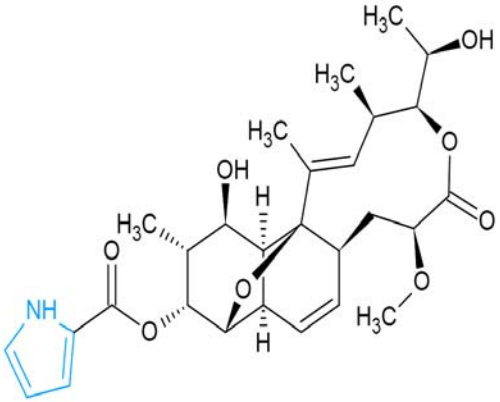
Scheme 6 – $La(OTf)_3$ catalyzed synthesis of α-aryl tetrasubstituted pyrrole derivatives.



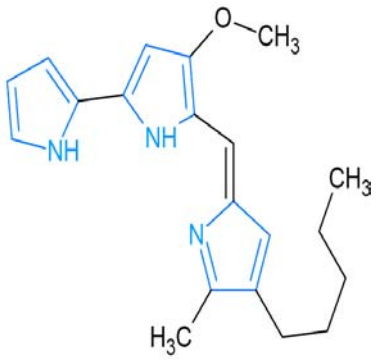
Indometacin (NSAID)



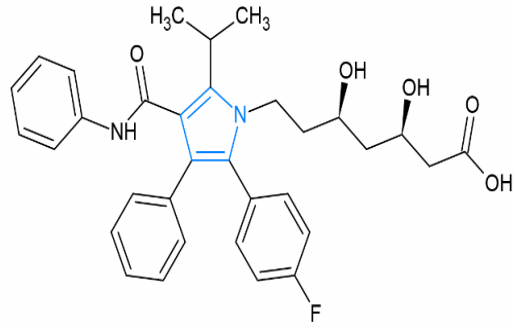
Tolmetin (NSAID)



Nargenicin (antibacterial drug)



Prodigiosin (anticancer, antimalarial, antibacterial and antifungal drug)



Atorvastatin (lipid-lowering drug)

Fig. 3 – Selected drugs containing pyrrole ring.

Therapeutic applications of pyrroles

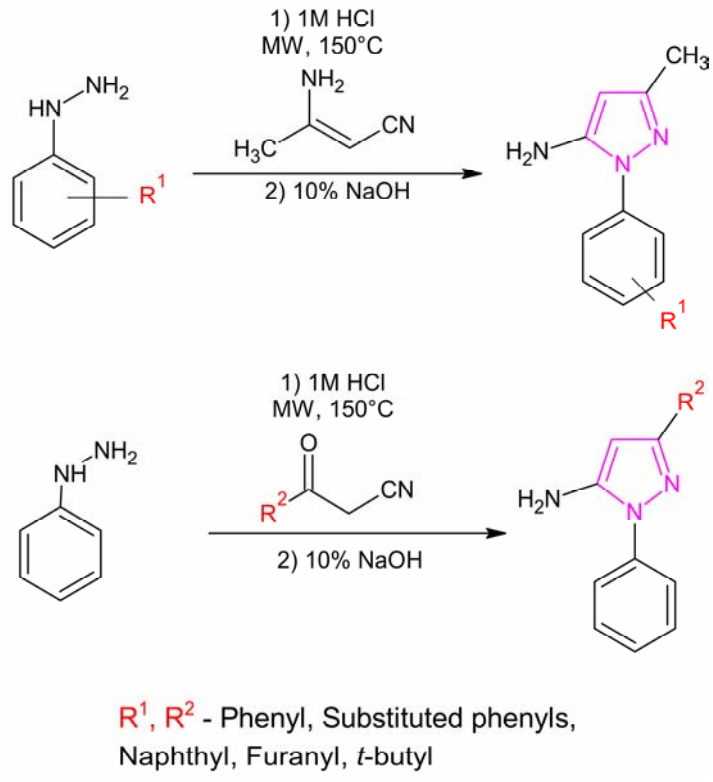
The high interest towards pyrrole containing heterocyclic substances is determined by the presence of this ring in the structure of various imported synthetic and natural compounds. Drugs possessing pyrrole moiety are known to act as anticancer, anti-inflammatory, anti-malarial, anti-microbial, anti-tubercular, anti-hypertensive and anti-ulcer agents.[27,28] Some molecules with pyrrole moiety are available in the pharmaceutical industry while other are in clinical trial. Thus Indometacin is a well known nonsteroidal anti-inflammatory drug (NSAID) that act as non-selective inhibitor of cyclooxygenase (COX-1 and COX-2) to treat chronic conditions such as rheumatoid arthritis, ankylosing spondylitis and osteoarthritis.[11] The widely applied Atorvastatin is a distinguished pyrrole drug used in patients with hypercholesterolemia (lipid-lowering drug included in the statin class of medications).[29] A representative of macrolides with an antibacterial activity, containing a pyrrole moiety is Nargenicin.[7] Another employed commercial drug with a pyrrole core is Tolmetin. It reduces the production of prostaglandins and it is applied in the treatment of rheumatoid arthritis and osteoarthritis. Prodigiosin contains three pyrrole rings and it is reported to possess anticancer, antimalarial, antibacterial and antifungal properties.[30,31] Furthermore, since 2015 pyrrole derivatives have been heavily examined for anticancer activity.[32] (**Figure 3**)

Reports of the MW applications in the synthetic protocols of the aforementioned active substances are steadily increasing. A paper discussing the MW irradiated synthesis of Indomethacin derivatives has been recently reported by Amin *et al.*[33]. In addition, MW-assisted syntheses of Tolmetin, Nargenicin and Prodigiosin analogues have also been examined.[34-36]

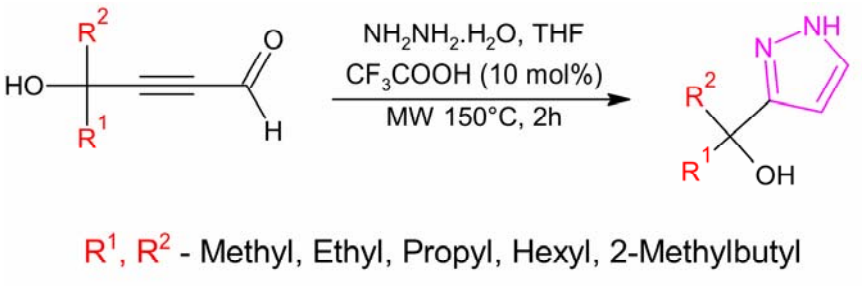
2. Pyrazole

Pyrazole and its derivatives play an important role in pharmaceutical chemistry. A lot of active molecules contain pyrazole ring in their structures. In the last years microwave synthesis of these drugs showed short reaction times, decrease of energy used, higher purity and higher yields.

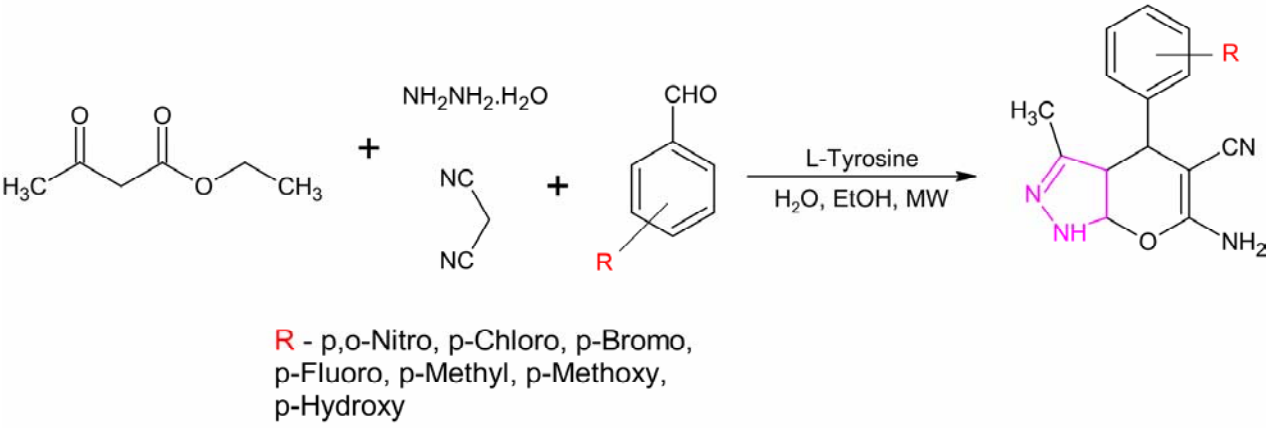
A recent application of the microwave irradiation has been described by Everson *et al.* (**Scheme 7**).[37] The reaction protocol has been defined as rapid (in the range of 10-35 min) and highly productive (with yields over 66%). The optimal conditions have been found to be 1M HCl with a 150°C MW heating. Water has been used as a "green" solvent. No purification of the final products has been conducted.



Scheme 7 – Microwave-assisted synthesis of 1*H*-pyrazole-5-amines.



Scheme 8 – One-pot synthesis of substituted pyrazole derivatives.



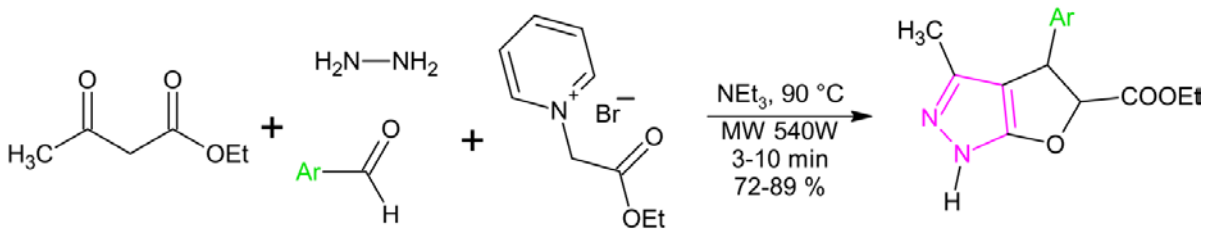
Scheme 9 – Multi-component synthesis of dihydropyrano[2,3-*c*] pyrazole derivatives.

Another synthetic protocol for the production of pyrazole derivatives by microwave irradiation has been developed by Bulanov *et al.* (**Scheme 8**).[38] The synthesis of the target pyrazoles was conducted by 1,2-nucleophilic addition of hydrazine to α-acetylenic γ-hydroxyaldehydes with further adduct cyclization. That approach has allowed the production of substituted pyrazole derivatives with moderate to high yields. Interestingly, the authors have reported that the reaction did not need any catalysts. Moreover, the specific use of propanol as a solvent has been pointed out as necessary due to the generation of side products when methanol has been utilized. The optimal temperatures have been discovered to be 150°C.

The multi-component synthesis of dihydro-pyrano[2,3-c] pyrazole derivatives by microwave irradiation has been reported by Rupnar *et al.* (**Scheme 9**).[39] The proposed "green" protocol includes water:ethanol as a solvent and L-Tyrosine as a catalyst. The optimal irradiation time has been considered to be 5 minutes. In addition, the authors have detected very high yields (86-94%) by applying both electron donating and withdrawing groups. The work has also provided a plausible mechanism for the formation of the pyrano[2,3-*c*]pyrazole based products. Overall, the mild reaction conditions, the obtained high yields and the inexpensive catalyst are some of the promising features of the aforementioned protocol.

A similar four-component reaction using microwave irradiation was developed by Tangeti *et al.* (**Scheme 10**).[40] The formation of the target dihydro-1H-furo[2,3-c]pyrazole derivatives is initiated by diastereoselective synthesis of β-keto ester, hydrazine, aromatic aldehyde, and pyridinium ylide in the presence of triethylamine. The protocol is associated with simple and efficient procedure, high atom economy, short reaction time, efficiency of producing two C–C and one C–O bonds, two stereocenters in a single operation and good yields. It has been discussed that the products obtained from electron-donating group situated at 4-position in the aldehydes required significantly lower reaction time compared to electron-donating group placed at the latter position. The reported reactions have been carried out in solvent-free environment, which further enhances the environmentally benign of the method. A possible mechanism has been proposed by the authors.

The discussed methods led to formation of a numbers of pyrazole-based biologically active compounds.



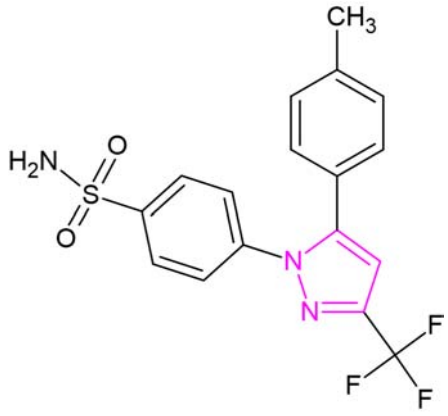
Ar - Substituted phenols, Furyl, Thiophenyl, 3-Pyridyl

Scheme 10 – Multicomponent one-pot synthesis of dihydro-1*H*-furo[2,3-*c*]pyrazole derivatives.

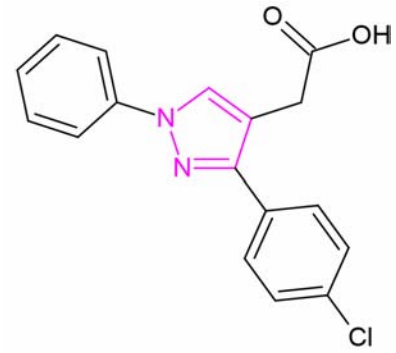
Therapeutic applications of pyrazoles

Pyrazole-based compounds are widely discussed and analyzed for their anti-inflammatory, anti-allergy, antiviral, antimicrobial, anticancer, antiepileptic, antitubercular properties.[41] Pyrazoles moiety is present in the first cyclo-oxygenase selective inhibitor – Celecoxib, initially introduced in 1998.[42] Since then, various celecoxib analogs have been synthesized and discussed.[43] Moreover, the pyrazole heteroring is an essential core structure of the anti-inflammatory drug Lonazolac,[44] the H_2 receptor agonist Betazole,[45] the treatment of erectile dysfunction and the pulmonary arterial hypertension drug Sildenafil.[46] Despres *et al.*[47] reported the effects of Rimonabant in the treatment of obesity. Rimonabant is a pyrazole derivative and it is selective cannabinoid-1 receptor antagonist. (**Figure 4**) Fomepizole (4-methylpyrazole) is utilized in the treatment of methanol and ethylene glycol poisoning.[48]

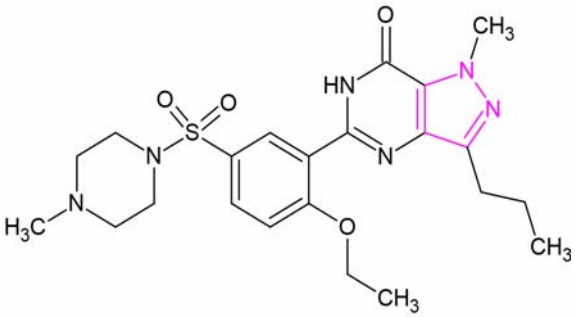
Numerous papers have reported the rapid syntheses of Celecoxib and Sildenafil derivatives after the utilization of MW irradiation.[49,50]



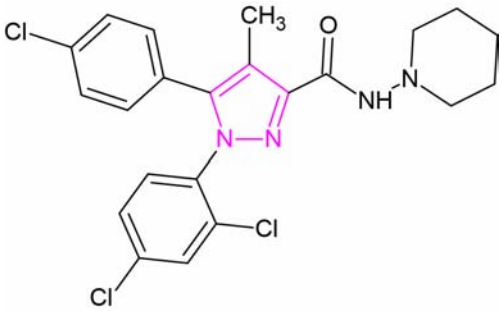
Celecoxib (COX-selective inxibitor)



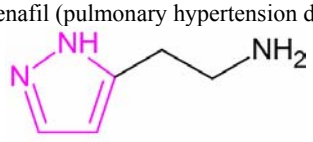
Lonazolac (anti-inflamatory drug)



Sildenafil (pulmonary hypertension drug)



Rimonabant (anorectic anti-obesity drug)



Betazole (histamine H_2 receptor agonist)

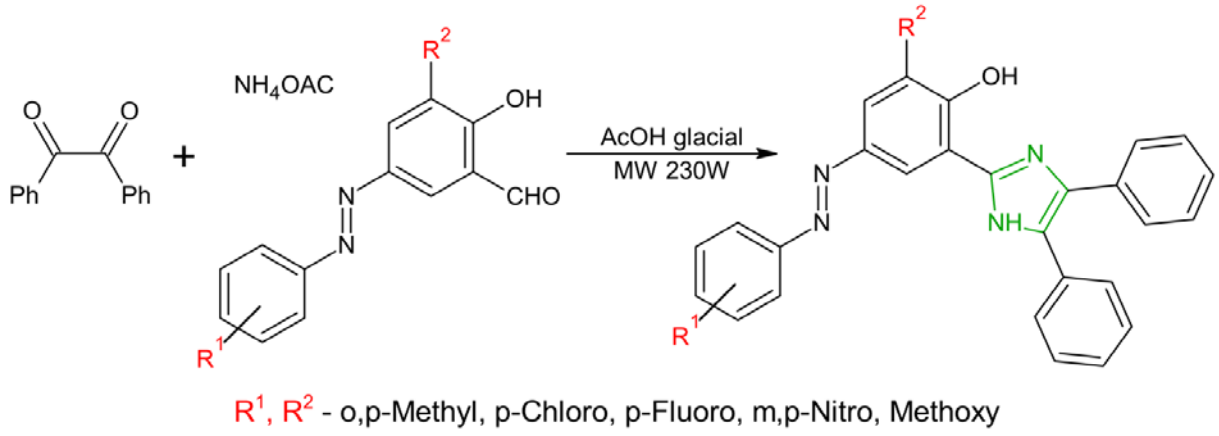
Fig. 4 – Selected drugs containing pyrazole ring.

3. Imidazole

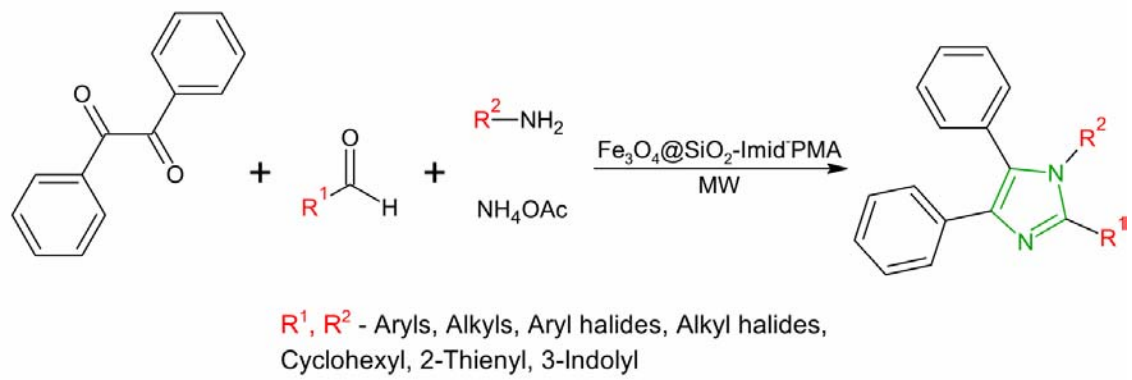
Imidazole is an important heterocyclic ring in functional molecules and is utilized in a diverse range of applications. The development of new methods for the microwave-assisted synthesis of substituted imidazoles is of strategic importance. It is due to their versatility and utility that expedient methods for the synthesis of imidazole derivatives are both highly topical and necessary.[51]

One-pot three-component microwave-assisted formation of novel azo-imidazoles has been described by Mahmoodi *et al.* (**Scheme 11**).[52] The paper has reported the incorporation of imidazole into an azo dye through microwave irradiated heating of azo dye, NH_4OAc and benzyl. The method has been optimized by altering the type of solvents, the organic catalysts and the heating conditions. The utilization of MW oven has been noted as the most prominent procedures for the described products. However, the authors underlined the importance of the glacial acetic acid as the most suitable solvent, while ethanol and chloroform have exhibited yields under 40%. A mechanism for the occurring nucleophilic attack, with further condensation and rearrangement to the azo-imidazole product, has been proposed.

Esmaeilpour *et al.* have reported the MW irradiated synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole applying magnetic catalyst (Fe_3O_4@SiO_2-ImidPMAn) (**Scheme 12**).[53] The key characteristics of the reaction method were the simplicity of operation, easy work-up, high yields and low reaction times due to the application of MW oven. In addition, no solvent was used which further increase the green aspect of the synthetic protocol. The paper has compared the MW synthesis with the conventional one and significant advantages of the MW-assisted synthesis were detected. The reaction times were lowered from 12 h to 10 min. Overall, the discussed paper demonstrates a suitable green protocol for the synthesis of substituted imidazoles.



Scheme 11 – Microwave-assisted synthesis of azo-imidazoles.

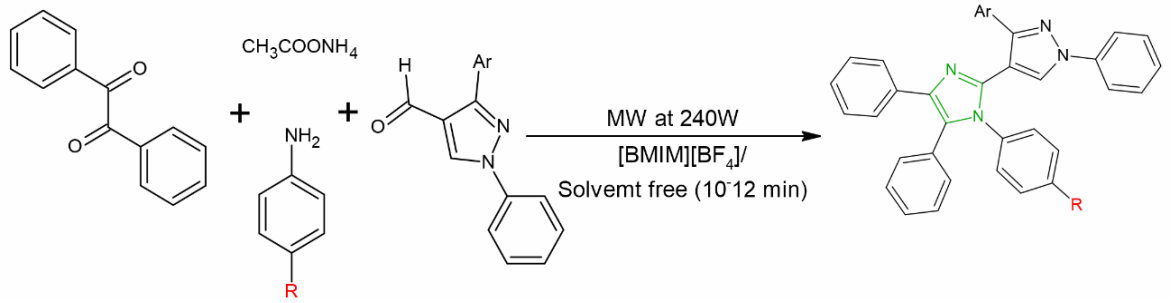


Scheme 12 – One-pot four component condensation reaction for synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives.

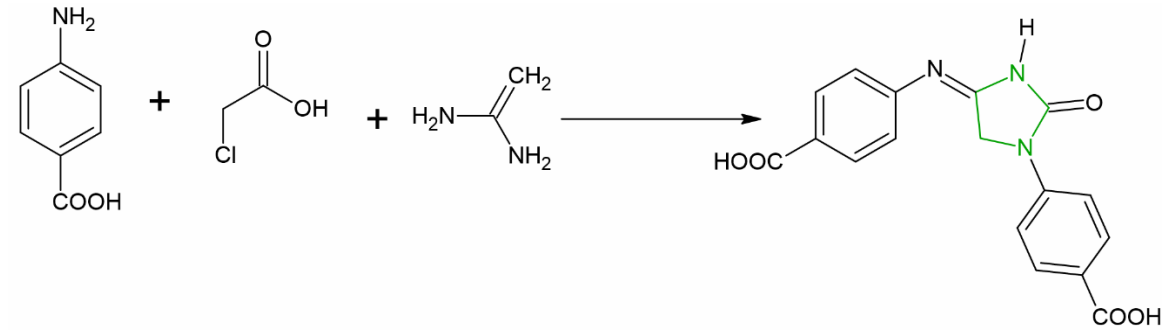
Two years later Shirole *et al.* applied green protocol for one-pot synthesis of tetrasubstituted imidazoles using similar reagents under microwave heating. Primary amine, benzyl, substituted carbaldehyde and ammonium acetate have been used for starting materials **(Scheme 13)**. [BMIM][BF_4] was used as a catalyst and the reactants were MW irradiated at 240W for 10 min. The same imidazoles were produced after conventional heating and the work concluded dramatically decreased reaction time when MW irradiation was utilized. Moreover, better yields were observed when electron-donating substituents were present in the pyrazole aldehyde compared to electron-withdrawing replacements.[54]

Selim *et al*. have designed a method for MW assisted synthesis of novel imidazoles. 4-aminobenzoic acid, urea and chloroacetic acid have been used to form the final products **(Scheme 14)**. The authors noted significant reduction of the reaction time when MW irradiation has been applied. Furthermore, cleaner products and higher yields were reported.[55] However, in one of the cases the MW irradiated synthesis could not produce the desired product, while the conventional methodology demonstrated success.

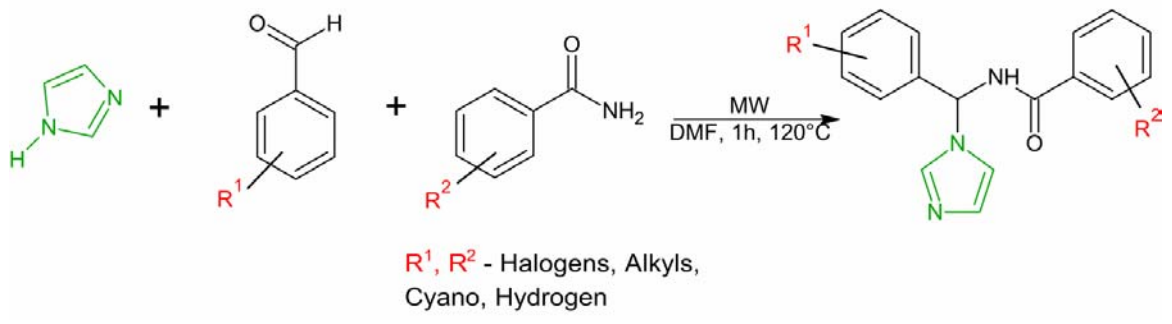
Recently Bai *et al.* have reported one-pot multicomponent reactions for the synthesis of imidazole derivatives through microwave-assisted approach (**Scheme 15**). Imidazole, benzaldehyde, and benzamide have been used as model starting reagents. The resulting imidazole derivatives were successfully obtained in moderate to good yields (52–87%).[56] The paper compared the MW-assisted and the conventional synthetic approaches. It has been observed that when MW irradiation was utilized the rate and yield of the reactions significantly increased. The reaction time dropped from 48 h to 0.5-2 min.



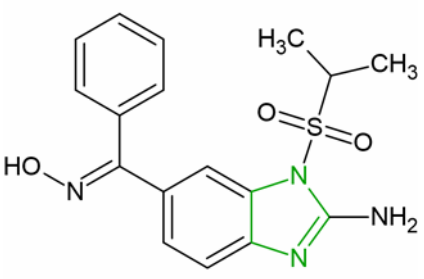
Scheme 13 – Microwave-assisted synthesis of 1,2,4,5-tetrasubstituted imidazoles.



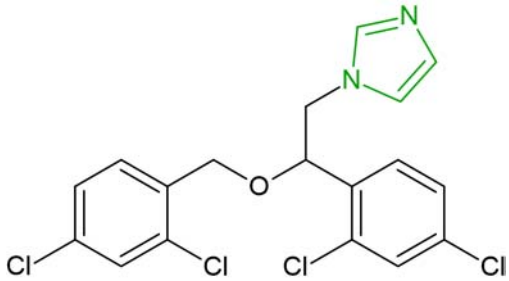
Scheme 14 – One-pot synthesis of imidazole derivatives.



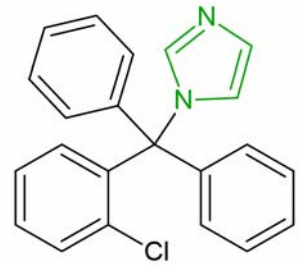
Scheme 15 – Multicomponent reaction for synthesis of imidazole derivatives.



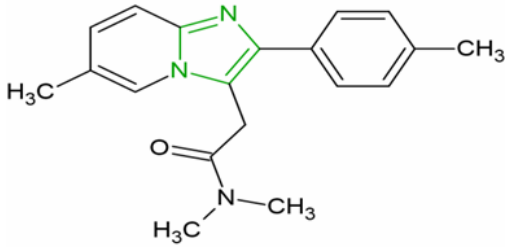
Enviroxime (antiviral drug)



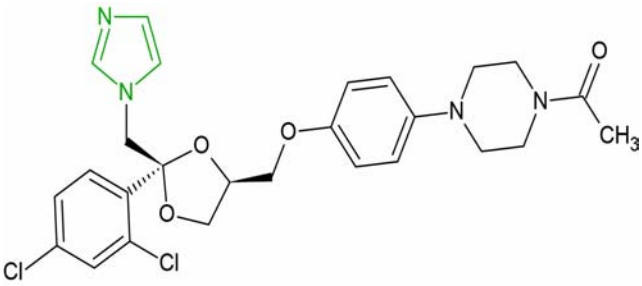
Miconazole (antifungal drug)



Clotrimazole (antifungal drug)



Zolpidem (hypnotic drug)



Ketoconazole (antifungal drug)

Fig. 5 – Selected drugs containing imidazole ring.

Therapeutic applications of imidazoles

Imidazole is a significant hetero group in many medicinal structures. It plays important role in the design of antiinflamatory, antibacterial, antifungal (like ketoconazole, miconazole, clotrimazole), antiviral (such as Enviroxime), hypnotic (like Zolpidem), antitubercular, anticoagulant and antidepressant drugs (**Figure 5**).[57] Recent paper, published by Greish *et al.*, has studied the anticancer activity of imidazole-based compounds.[58] HO-1 inhibitory activity has been reported and further ADME prediction has been made. Moreover, imidazoles have been applied in the therapeutic scheme for Chagas disease.[59] Few papers have been posted on the antihypertensive effect of imidazole derivatives.[60,61] Some imidazole compounds have biological activity on insects and are used as agrochemicals.[62] Imidazole group can also have pharmacological activity as antidiabetic agent, an anticonvulsant agent, immune suppressant, anesthetic, thromboxane synthase inhibitor, antithyroid agent, blocker of retinoic acid metabolism, sedative agent and analgesic.[11]

Out of all discussed compounds, available reports for the implementation of MW heating for the syntheses of clotrimazole, ketoconazole and zolpidem have been found.[63-65]

4. Triazole

4.1. 1,2,3-Triazole

1,2,3-triazoles are extremely stable compounds with a diverse set of pharmacological activities. They are highly soluble and have elevated affinity towards bioreceptors considering the potential for hydrogen bond formation, dipole-dipole and p-stacking interactions.[66]

There are two tautomeric forms of 1,2,3-triazoles: 1*H*-1,2,3-triazole and 2*H*-1,2,3-triazole as given on **Figure 6**.[67]

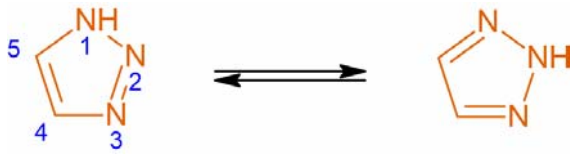
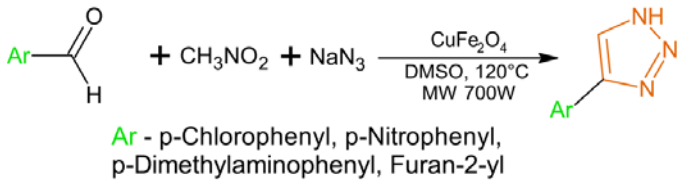


Fig. 6 – Tautomeric forms of 1,2,3-triazole.

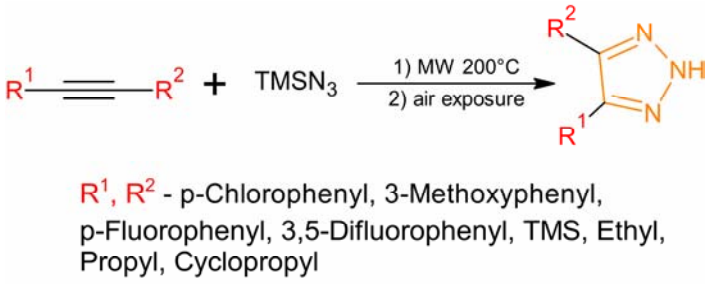
Bhuyan *et al.* have developed a simple operating procedure for synthesis of 4-aryl-1*H*-1,2,3-triazoles starting from aromatic aldehydes, sodium azide and nitromethane. The reaction proceeds under microwave irradiation using magnetically active $CuFe_2O_4$ catalyzed cascade. This synthetic approach is characterized by a short reaction time (5-10 min.), wide substrate scope, reusability of the catalyst, satisfactory to high product yield (60-97%). (**Scheme 16**).[68]

Roshandel *et al*. reported a solvent free, catalyst-free, and additive-free synthesis of 1,2,3-triazoles in good to excellent yields through the cycloaddition of trimethylsilylazide and acetylenes. This method can be applied for both aromatic and aliphatic terminal alkynes. This study also shows the effect of polarity and spatial interference on overall yield and reaction time using different symmetric and asymmetric internal alkynes. Polar molecules selectively absorb microwave radiation while nonpolar molecules remain inert to it. Therefore, a shorter reaction time can be observed with increasing number of polar groups. (**Scheme 17**).[69]

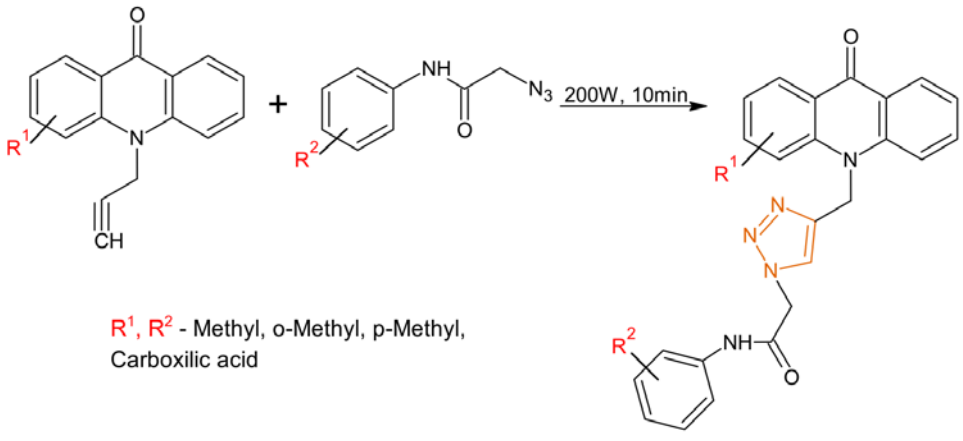
Recent paper published by Aarjane *et al.* has discussed the microwave assisted synthesis of acridone-1,2,3-triazole derivatives (**Scheme 18**). Azide-alkyne cycloaddition has been carried out in MW oven using $CuSO_4.5H_2O$/NaAsc as a catalytic system and water:*t*-BuOH (1:1) as a solvent at room temperature. Several solvents (DMF, DMF/H_2O and CH_2Cl_2) were used for the optimization of the reaction. It was concluded that dimethylformamide produced optimal product yield. Reaction times were ranging from 10 to 15 min when MW irradiation was applied. However, the classical approach significantly increases the duration of the process.[70]



Scheme 16 – Synthesis of 4-Aryl-1*H*-1,2,3-triazoles from aromatic aldehydes, sodium azide and nitromethane.



Scheme 17 – Reaction of trimethylsilyl azide with various acetylene substrates.

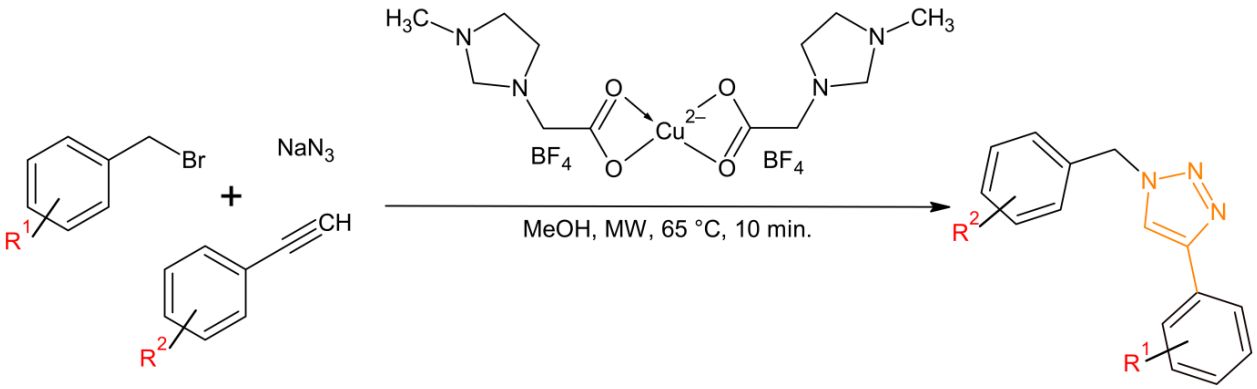


Scheme 18 – Synthesis of acridone-1,2,3-triazole derivatives.

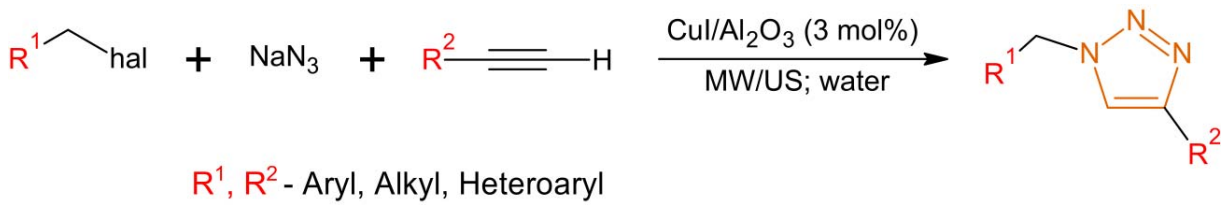
Saikia *et al*. have developed one pot synthesis of 1,4-disubstituted 1,2,3-triazoles using MW oven. This synthesis takes place in two stages. Initially, azide is formed by the reaction of substituted benzyl bromide with NaN_3 in methanol. The azide obtained from the first step is then reacted with a terminal alkyne in the presence of a Cu (II) catalyst supported by an ionic liquid to generate the corresponding 1,4-disubstituted 1,2,3-triazole. The reaction time is 8-10 minutes and the yields of the obtained compounds are from 85% to 95%. (**Scheme 19**).[71] A similar synthetic approach of 1,4-disubstituted 1,2,3-triazoles was described by Agalave *et al.* They used a neutral alumina-supported copper iodide catalyst. The advantages of this catalyst are that it can be prepared very easily and in a short time, forming the only desired product, and on the other hand there is no contamination with copper in the product. The authors have found that this catalyst can be recovered and reused without noticeable loss of activity. Allyl or benzyl halides, sodium azide and terminal alkynes have been involved to form the final products. The obtained compounds are in yields 98% yields (**Scheme 20**).[72]

Souza *et al.* have applied efficient method for synthesis of new imine 1,4-disubstituted 1,2,3-triazoles. The procedure has been developed based on a multicomponent reaction under microwave-assisted conditions involving α-thio aldehyde and propargylamine, with the formation of an imine that *in situ* reacts with organoazides by copper-catalyzed [3+2] azides–alkyne cycloaddition (CuAAC). The reaction results in a small library of imine 1,4-disubstituted 1,2,3-triazoles (**Scheme 21**). The products were obtained in 57% to 83% yield.[73]

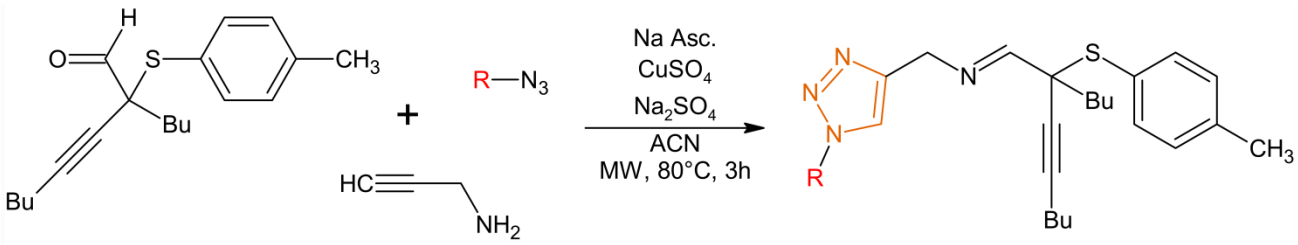
Narsimha *et al*. have developed one-pot microwave-assisted synthesis of fused 1,2,3-triazole derivatives from 1-iodoalkynes with different aryl azides. After a series of studies, the authors reach the optimal conditions that are the CuI catalyst (10 mol%) with 2 equivalents of t-BuOK in [Bmim] PF6 under microwave irradiation (150 W). The obtained desired products have good to excellent yields. (**Scheme 22**).[74]



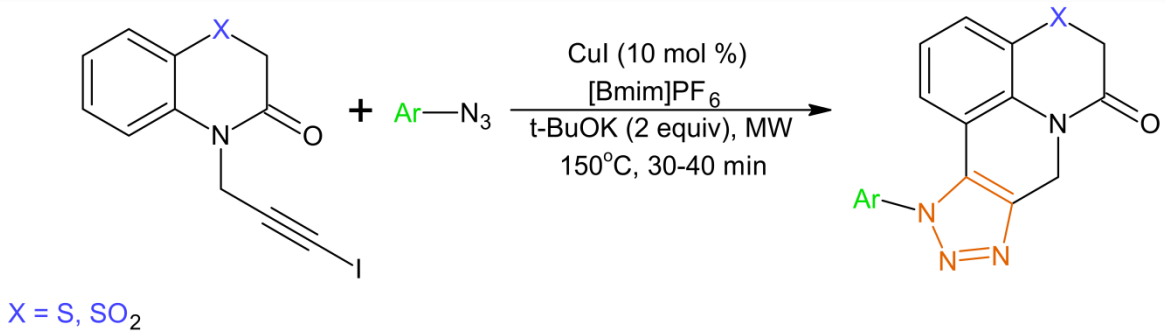
Scheme 19 – Multicomponent synthesis of 1,4-disubstituted 1,2,3-triazoles using ionic liquid supported Cu(II) catalyst.



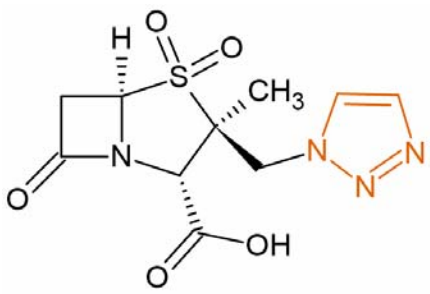
Scheme 20 – Microwave-assisted synthesis of 1,4-disubstituted 1,2,3-triazoles catalyzed by CuI on Al_2O_3.



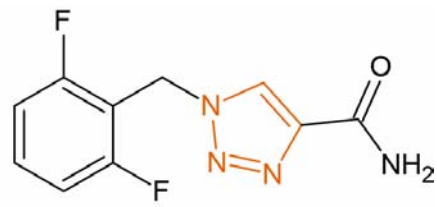
Scheme 21 – Microwave-assisted three-component synthesis of imine 1,2,3-triazole derivatives.



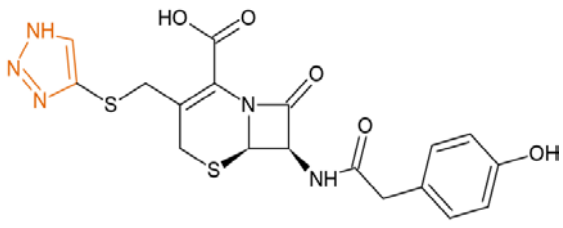
Scheme 22 – One-pot synthesis of fused 1,2,3-triazoles from 1-iodoalkynes with different aryl azides.



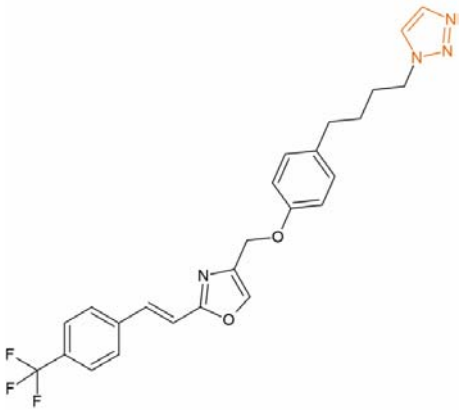
Tazobactam (*beta*-lactam antibiotic)



Rufinamide (anticonvulsant drug)



Cefatrizine (*beta*-lactam antibiotic)



Mubritinib (anticancer drug)

Fig. 7 – Selected drugs containing 1,2,3 triazole ring.

Therapeutic applications of 1,2,3-triazoles

1,2,3-triazoles have a wide variety of pharmacological properties. Important utilization of the structures with 1,2,3-triazoles moiety is in the field of antitumor therapy (such as Mubritinib).[75] One of the first reports for the alkylating properties of 1,2,3-triazole derivatives was published by de la Heras *et al.*[76] Recently hybrid forms of 1,2,3-triazoles have been synthesized and examined for anticancer activity.[77-80] Few QSAR studies have given an insight into structure-activity relationship of 1,2,3-triazoles and their cytotoxic effects.[81] Furthermore, anti-tubercular,[82,83] antiparasitic,[84] antiviral,[85] anti-inflamatory[86] effects of compounds with a 1,2,3-triazole systems have also been reported. The 1,2,3-triazole moiety is present in the structures of the *beta*-lactams antibiotics Tazobactam and Cefatrizine.[87] Rufinamide used as an anticonvulsant also contains a 1,2,3-triazole ring (**Figure 7**).[88]

4.2. 1,2,4-Triazole

Recently the interest in 1,2,4-triazoles and its hybridization structures with wide variety of heterocycles is emerging as a prominent one.[89] There are two tautomeric forms of 1,2,4-triazoles of which 1*H*-1,2,4-triazole is more stable than 4*H*-1,2,4-triazole as given in **Figure 8**.[90]

Many synthetic methods have been discussed for the preparation of 1,2,4-triazoles such as reaction of nitriles and hydrazonoyl chlorides[91] reaction of amides or thioamides with hydrazides (Pellizzari reaction), reaction of imides with alkyl hydrazines (Einhorn–Brunner reaction)[92] and many others, but these methods required long reaction time, expensive reagents and are often multistep processes. In the last years microwave-assisted synthesis showed short reaction times, minimal side reactions and improved yields.[93]

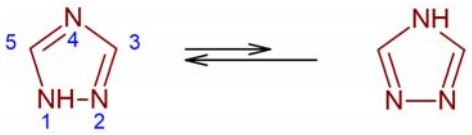
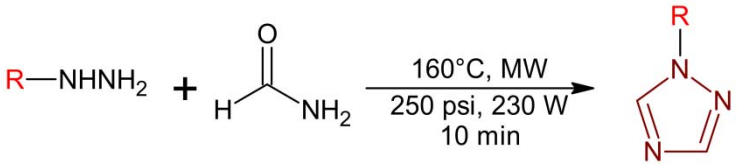


Fig. 8 – Tautomeric forms of 1,2,4-triazole.

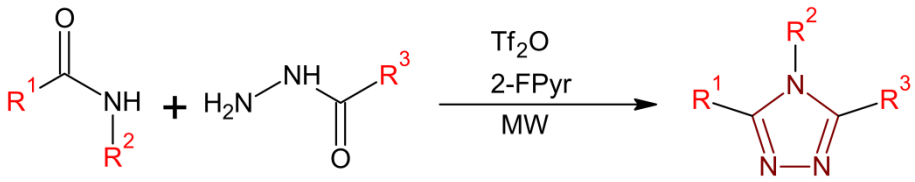
Shelke *et al*. have described an efficient microwave irradiation for synthesis of substituted 1,2,4-triazole derivatives. Variously substituted aryl or alkyl hydrazines react with formamide, catalyst-free to obtain compounds in moderate to good yield. The short reaction time and excellent tolerance to functional groups are the main advantages of this method. (**Scheme 23**).[92]

Bechara *et al*. described a one-pot process for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles (27-89%) by the reaction of secondary amides with hydrazides. This reaction is activated by triflic anhydride, followed by microwave-induced cyclodehydration (**Scheme 24**).[94]



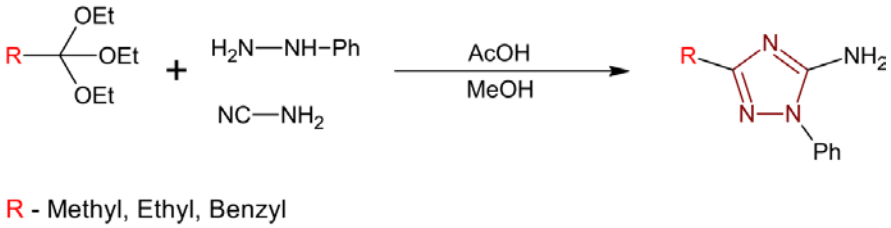
R - Phenyl, p-Methoxyphenyl, 2-MethylPhenyl, 3-FluoroPhenyl, 2-Chlorophenyl, 3-Chlorophenyl, 2,4-Dichlorophenyl, 4-Bromophenyl

Scheme 23 – One-pot catalyst-free synthesis of 1,2,4-triazole derivatives.



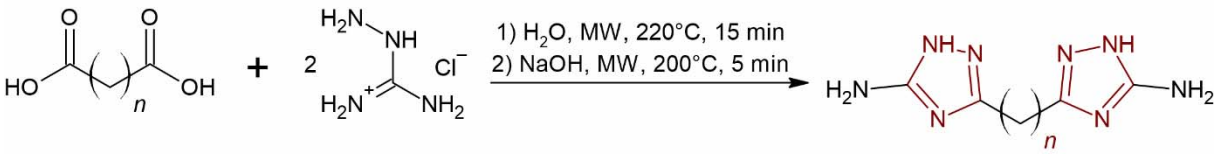
R^1, R^2, R^3 - Phenyl, 2-Methoxyphenyl, p-Methoxyphenyl, Cyclohexane, 3-Fluorophenyl, 2-Methylphenyl, Isopropyl, p-Bromophenyl

Scheme 24 – Tf_2O-mediated synthesis of 3,4,5-trisubstituted 1,2,4-triazole derivatives.

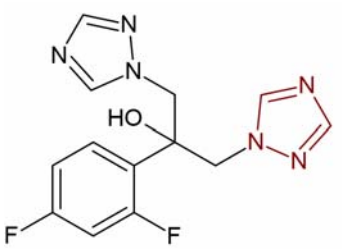


R - Methyl, Ethyl, Benzyl

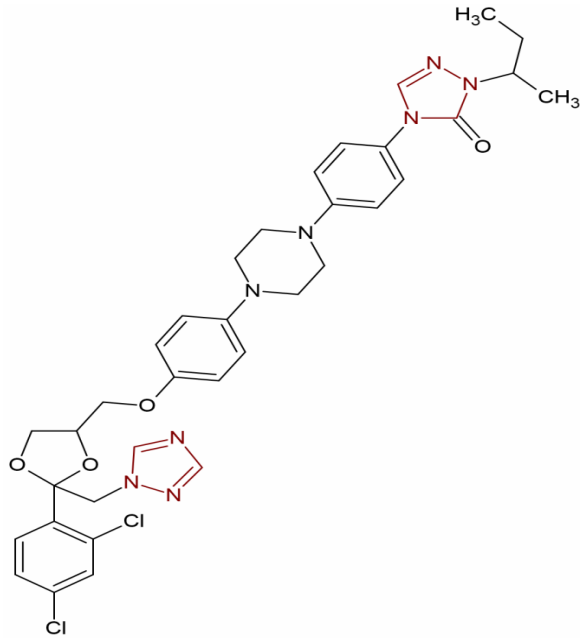
Scheme 25 – Microwave-assisted synthesis of 1,2,4-triazole derivatives.



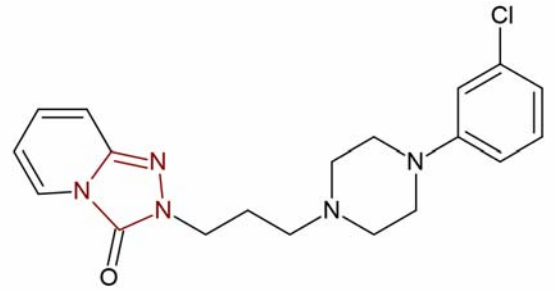
Scheme 26 – Microwave-assisted synthesis of polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines).



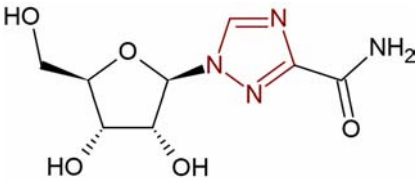
Fluconazole (antifungal drug)



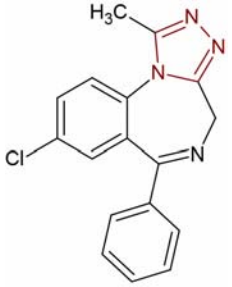
Itraconazole (antifungal drug)



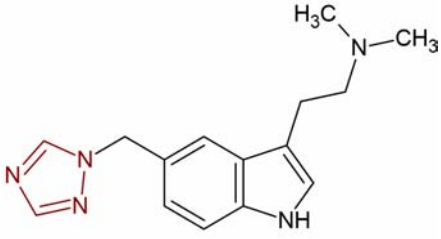
Trazodone (antidepressant drug)



Ribavarin (antiviral drug)



Alprazolam (anxiolytic drug)



Rizatriptan (antimigraine drug)

Fig. 9 – Selected drugs containing 1,2,4 triazole ring.

Aouali *et al.* adopted a one-pot procedure to produce 5-amino-1-phenyl-1,2,4-triazole derivatives under microwave irradiation with high yields. For this multicomponent reaction, orthoester, phenylhydrazine and cyanamide have been used for starting materials. Reaction times were 40 min (200 W, 80°C). The obtained derivatives were with better yields and higher purity of the products, when MW irradiation was applied. However, the classical approach significantly increases the duration of the process (48 h). (**Scheme 25**).[95]

An interesting highly selective and efficient microwave irradiation method for 3,3'(5,5')-polymethylene-bis (1*H*-1,2,4-triazol-5(3)-amines) synthesis is described by Lim *et al.* Various dicarboxylic acids react with aminoguanidine hydrochloride in aqueous medium at 220°C for 15 minutes, followed by the addition of an aqueous solution of sodium hydroxide and microwave irradiation at 200°C for 5 min. The obtained compounds have good yields and high purity. (**Scheme 26**).[96]

Therapeutic applications of 1,2,4-triazoles

Various drugs with a 1,2,4-triazole moiety have been synthesized and implemented in the pharmaceutical industry. The presence of 1,2,4-triazole scaffold results in antihypertensive, antibacterial, anticonvulsant, anti-inflammatory and antitumor activity.[97-101] Some of the most widespread drugs with a 1,2,4-triazole structure are the antifungal drugs Itraconazole, Fluconazole, Voriconazole, Tebuconazole.[102] Other commercially available drugs with 1,2,4-triazole moiety are Alprazolam, Estazolam, Triazolam (anxiolytic, sedative, tranquilizer effect), Rizatriptan (treatment of migraine headaches), Trazodone (antidepressant), Letrozole, Anastrazole (nonsteroidal competitive aromatase inhibitors) and Ribavarin (antiviral).[103] (**Figure 9**)

A lot of papers have confirmed for microwave-assisted syntheses of Fluconazole, Ribavirin and Trazodone analogues.[104-106]

5. Tetrazoles

Tetrazole is a five membered heterocyclic compound, consisting of four nitrogen atoms and one carbon atom. There are two tautomeric forms of tetrazole – 1*H*-tetrazole and 2*H*-tetrazole.

Due to the widespread use of tetrazole in medicinal chemistry, its synthetic flexibility is extremely important.

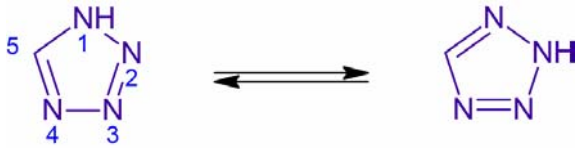


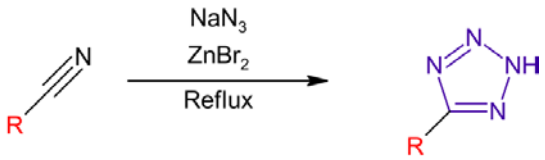
Fig. 10 – Tautomeric forms of tetrazole.

The most common method for the synthesis of tetrazoles is the (3+2) cycloaddition of nitriles with sodium azides. The reaction was first carried out by Demko *et al.* (**Scheme 27**).[107] They carry out the reaction in the presence of zinc salts, using water as a solvent. This safe and extremely effective process with a reaction time of 2-48 h resulted in the production of 5-substituted 1*H*-tetrazoles in a yields of 64-96%.

The papers cited below have demonstrated a significant reaction time reduction when MW irradiation had been involved in the process of the tetrazole synthesis.

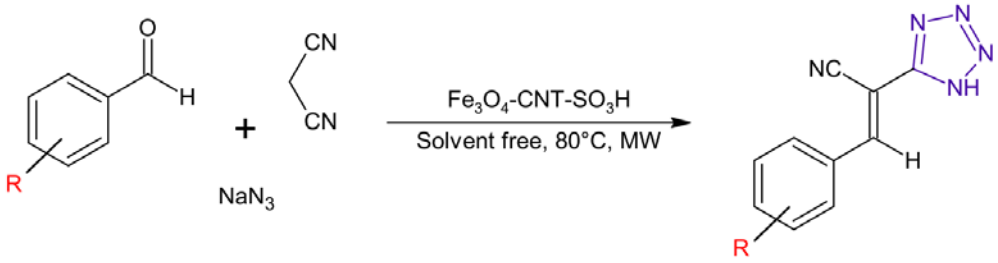
Akbarzadeh *et al.*[108] have reported for highly efficient and ecofriendly microwave synthesis of 5-substituted-1*H*-tetrazoles via multicomponent domino Knoevenagel condensation/1,3-dipolar cycloaddition reaction using Fe_3O_4 magnetic nanoparticles as catalyst. Aromatic aldehydes, sodium azide and malononitrile have been utilized as starting reagents. The advantages of this procedure are inexpensive, nontoxic and recyclable catalyst, elimination of toxic and volatile solvents, short reaction time (35 min), easy methodology and excellent product yield. The authors have noted that the MW irradiation led to significant reduction of the reaction time, mild reaction conditions and overall cleaner procedure compared to conventional heating. (**Scheme 28**)

Recent work of Joshi *et al*. has demonstrated the MW assisted synthesis of novel 5-substituted 1H-tetrazoles in high yields through [3+2] Huisgen cycloaddition.[109] Various nitriles and sodium azide are used as starting materials. The reaction is catalyzed by a heterogeneous catalyst based on Cu (II). This catalyst can be reused without significant loss of catalytic activity up to five consecutive cycles. The desired tetrazoles were obtained by employing controlled microwave heating (230°C) within 3-30 min in the presence of N-Methyl-2-pyrrolidone as solvent. The advantages of this method are simple work-up procedure, short reaction time and recyclability of the catalyst. (**Scheme 29**)



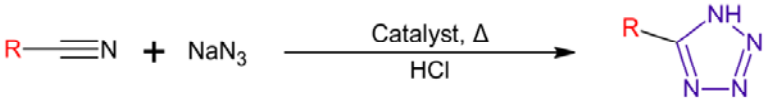
R - Aryl, Alkyl, Vinyl

Scheme 27 – Synthesis of 5-substituted 1*H*-tetrazoles from nitriles in water.



R - Hydrogen, p-Chloro, 2-Chloro, p-Fluoro, p-Nitro

Scheme 28 – Microwave-assisted synthesis of 5-substituted-1*H*-tetrazoles.



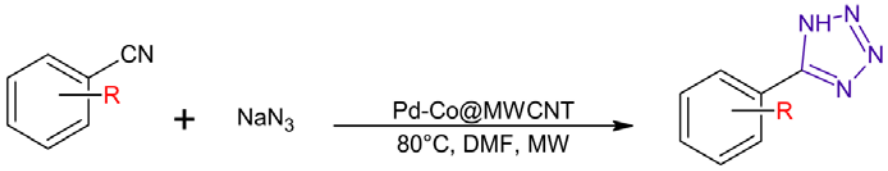
R - Phenyl, p-Chlorophenyl, 4-Trifluoromethylphenyl, p-Hydroxyphenyl, Furan-2-yl, 4-methylphenyl, p-Chlorobenzyl, 2-Naphthyl

Scheme 29. Synthesis of 5-substituted-1*H*-tetrazole derivatives.

In recent years, a number of similar approaches have been observed for the synthesis of 5-substituted 1*H*-tetrazoles using various nitriles and sodium azide as starting reagents. It is interesting to note that the individual authors used different catalysts in order to obtain high yield compounds in a short reaction time.

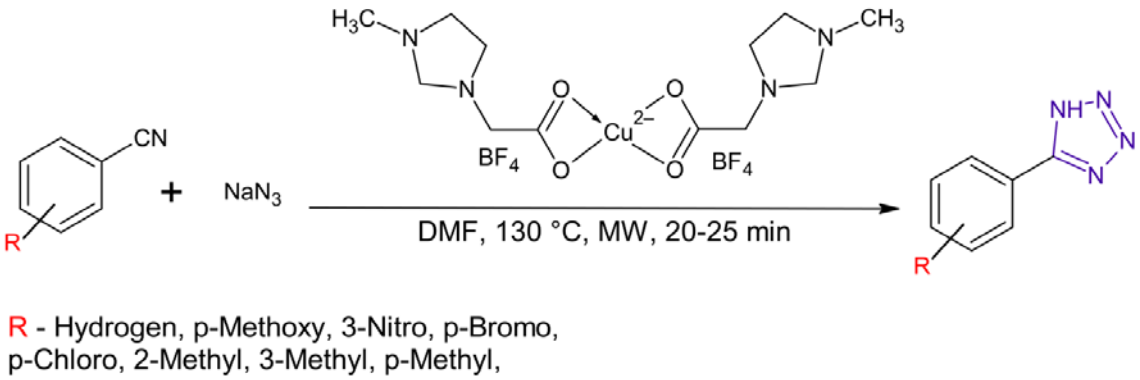
A study published by Yıldız *et al.*[110] has expanded the scope of novel catalyst which could be used in MW irradiated synthesis of 5-substituted 1*H*-tetrazoles. The paper has demonstrated the environmentally friendly and highly efficient utilization of Pd/Co nanoparticles in the process of MW assisted synthesis of 1*H*-tetrazoles. Ten distinct nitrilies have been applied as starting reactants and the yield of the corresponding tetrazole derivatives has been ranging from 90 to 99%. (**Scheme 30**)

Ionic liquid-supported Cu(II) has been defined as stable, eco-friendly and easy to prepare catalyst for the microwave assisted synthesis of 5-substituted 1*H*-tetrazoles.[111] Furthermore, the catalyst has been described as easily removable from the mixture with organic solvent. The synthesis was performed under both conventional heating and microwave irradiation, but the authors noted a significant increase in the reaction time in the conventional method. (**Scheme 31**)

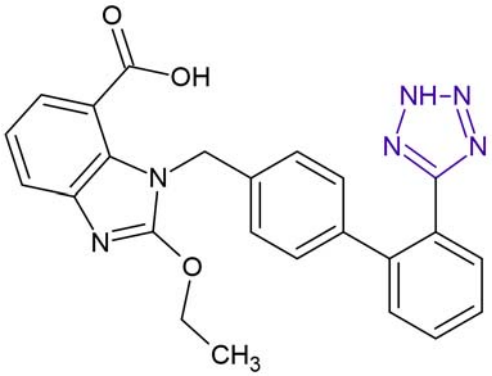


R - Phenyl, p-Nitrophenyl, p-Bromophenyl, p-Chlorophenyl, p-Methylphenyl, Pyridine-4-yl, p-Acetamidophenyl

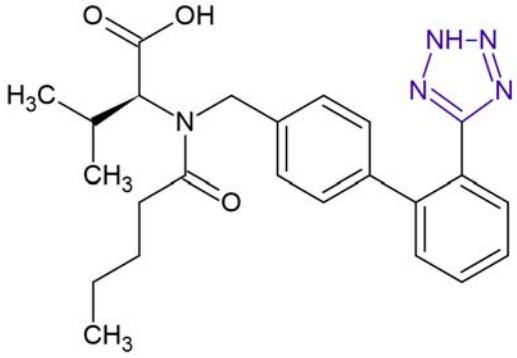
Scheme 30 – Microwave irradiated synthesis of 5-substituted 1*H*-tetrazoles.



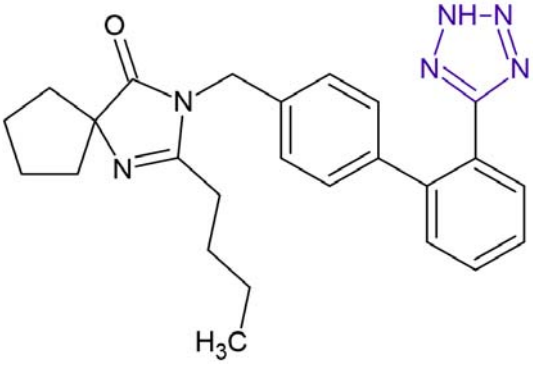
Scheme 31 – Microwave-assisted synthesis of 5-substituted 1*H*-tetrazoles using ionic liquid supported Cu(II) catalyst.



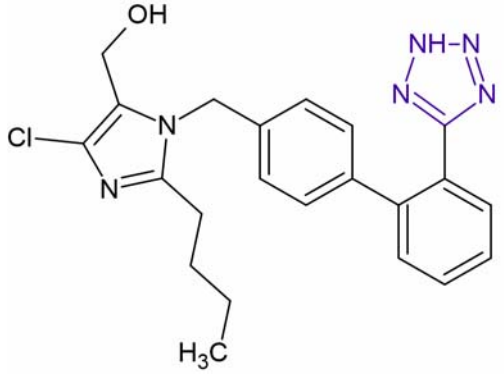
Candesartan (antihypertensive drug)



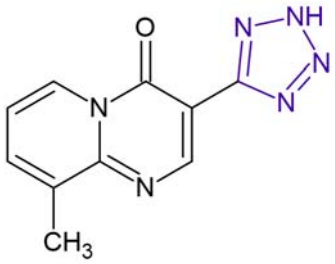
Valsartan (antihypertensive drug)



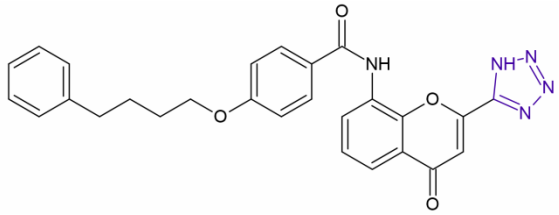
Irbesartan (antihypertensive drug)



Losartan (antihypertensive drug)



Pemirolast (antihistaminic drug)



Pranlukast (antihistaminic drug)

Fig. 11 – Selected drugs containing tetrazole ring.

Therapeutic applications of tetrazoles

Tetrazole and its derivatives have numerous pharmacological activities such as antibacterial (such as Cefazolin, Cefamandole, Ceftezole), antifungal, analgesic, anti-inflammatory, antidiabetic, anticancer and hypoglycemic activities.[112,113] Tetrazole moiety is essential for the angiotensin II antagonizing activity

of Candesartan, Losartan, Valsartan and Irbesartan.[114, 115] Other drugs containing a tetrazole ring are Pemirolast (mast cell stabilizer) and Pranlukast (cysteinyl leukotriene receptor-1 antagonist) used in therapy as an antihistaminic agent (**Figure 11**).[116]

Out of all discussed compounds, available reports for microwave-assisted syntheses of Irbesartan have been found.[117,118]

CONCLUSION

The need for rapid and greener synthetic approach towards the production of the important nitrogen containing heterocompounds is emerging as a main topic in recent years. This short review undoubtedly showed the significant advantages of MW assisted synthesis, of the nitro heterocycles, over conventional heating. The fast reaction times and generally higher yields are major appeal for organic chemists. Furthermore, the implementation of the MW irradiation could remove the need of a solvent as demonstrated in some papers. Thus, cleaner reactions are carried out and green chemistry protocols could be obtained. Applying MW irradiation has clearly turned into essential practice in medicinal chemistry since it drastically shortens the synthetic part of the drug discovery process.

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