1,2,3-Triazoles: A Review on Current Trends in Synthetic and Biological Applications

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Abstract: *The chemistry of 1,2,3-triazoles gained much attention since the discovery by Pechmann, since then several protocols have been developed for the synthesis of 1,2,3-triazoles, but after the copper catalyzed alkyne-azide cycloaddition (CuAAC) reaction, the mainly because of Huisgen's 1,3-dipolar cycloaddition reactions, it has evolved to become one of the most successful connective linkers and functional heterocyclic cores in modern organic chemistry. This review summarizes the up-to date developments in the synthetic methodologies and their biological applications, in particular of antimicrobial, anticancer, anti-inflammatory, anti-proliferative, antidiabetic properties of 1,2,3-triazoles. Also, the progress in the molecular hybridization; and physic-chemical properties have been highlighted.*

I. Introduction

Five membered heterocycles occupies prime place in synthetic and bioorganic chemistry. 1,2,3-Triazoles, a five-membered ring *N*-heterocycles, are main structural moieties in well-designed materials, pharmaceutical agents, bioactive products, synthetic intermediates, and in the research of life sciences and pharmaceuticals for their spacious applications. The need to steer the development of the synthesis of 1,2,3-triazoles toward more sustainable synthesis is a pressing issue [1]. The birth of click chemistry and the discovery of the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) led to the enormous growth in the field of 1,2,3-triazole chemistry and biology. 1,3-Dipolar azide-alkyne cycloaddition (AAC) reaction, often referred to as click reaction, is an expeditious and robust protocol for the construction of triazole derivatives. Non-conventional microwave heating has been used for the reaction showing ample advantages over the conventional thermal heating. Although 1,3-dipolar cycloaddition reaction of CuAAC was regarded as promising route for the synthesis of 1,2,3-trizoles, still the synthesis of relatively simple, high yielding with purity and accessible procedure needs to be developed. In recent years, several review articles have reported on the synthesis of 1,2,3-triazole derivatives [2, 3].

The present review article focuses on the developments in the synthesis and their medicinal applications. In particular, it was mainly focused on the synthesis involving the reactions of alkynes-organic azides, alkynes-aryl/alkyl halides, alkenes-organic azides, alkene-sodium azides, aldehydes and other notable protocols. The medicinal applications associated with 1,2,3-triazoles, particularly of antimicrobial, anticancer, anti-proliferative, anti-inflammatory, anti-diabetic and some other important activities. The review also focuses on the utility of 1,2,3-triazole core as scaffold in the transformation in to biologically potent 1,2,3-triazole-heterocycle molecular hybrids, and physic-chemical properties of triazole derivatives. The collection and compilation of synthesis methodologies of 1,2,3-triazole and biological applications in single platform is supportive and crucial for synthetic chemist to extend the diversity of the synthesis of 1,2,3-trizoles and biologists to study their pharmaceutical potencies.

II. Synthesis Of 1,2,3-Triazoles

2.1 From alkynes and an organic azide

Alkynes are useful scaffolds and are extensively used as precursors in the synthesis of isoxazoles [4,5], pyrazoles [6-8], triazoles, etc. In particular, an alkyne with organic azides are versatile substrates for the synthesis of triazoles, and the cycloaddition reactions involving these two components are the most important protocol for the preparation of heterocycles. The click-chemistry approaches based on 1,3-dipolar cycloaddition reaction known as Huisgen azide-alkyne method like copper catalyzed azide-alkyne cycloaddition (CuAAC), and Ruthenium catalyzed azide-alkyne cycloaddition (RuAAC) are particularly attractive and have received enormous attention over the recent years due to their utility in synthesis with diverse applications, from drugs to linkers for bio-conjugation. For instance, the beauty of this reaction is it needs two simple building blocks, an azide and an alkyne was completely discussed by Totobenzara *et al* (Scheme 1) [9, 10]. Neto and co-workers reviewed the use of copper catalysts as well as other transition metals, such as gold, iridium, iron, nickel,

ruthenium, samarium, silver, and zinc catalysts in cycloaddition reactions, which heralded in significant development in the synthesis of triazoles [11].


Scheme 1
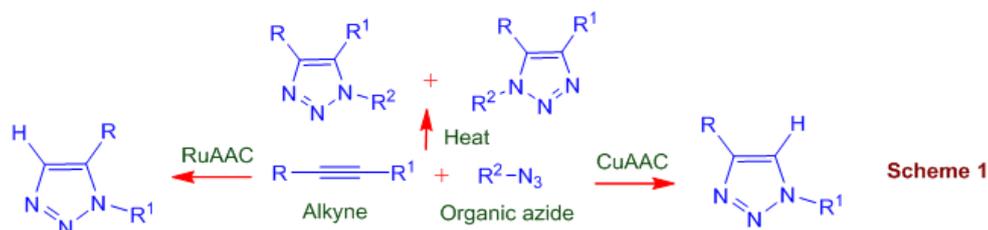
Wu and co-workers [12] reported the convenient synthesis of 1-substituted-1,2,3-triazoles from the corresponding aromatic and aliphatic azides in the presence of acetylene gas using mild, copper(I)-catalyzed 'click chemistry' involving CuI and triethylamine in DMSO solvent at room temperature. Shao *et al* [13] demonstrated the utility of both acid-base jointly promoted copper(I)-catalyzed azide-alkyne cycloaddition for the synthesis of 1,2,3-triazole derivatives. Bakherad *et al* [14] developed an efficient method for the synthesis of 1,2,3-triazole-linked benzimidazole through a copper-catalyzed click reaction in ethanol at 50°C. Method involves the reaction of a wide range of aromatic azides with *n*-propynylated benzimidazole *via* copper-catalyzed azide-alkyne cycloaddition reactions in the absence of a ligand (Scheme 2). The method offers many advantages including short reaction times, low cost, and simple purification procedures.


Scheme 2
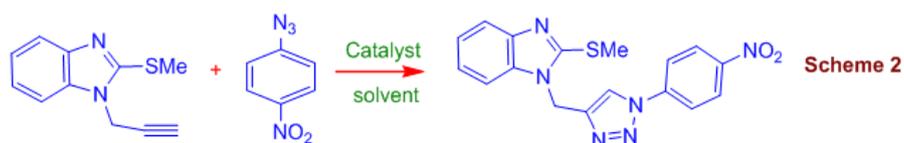
Metal-free 1,3-dipolar cycloaddition reactions have proven to be a powerful tool for the assembly of key heterocycles, in particular diversely functionalized 1,2,3-triazoles. A number of metal-free (3+2)-cycloaddition approaches have been developed up to date with the aim to circumvent the use of metal catalysts allowing these reactions to take place in biological systems without perturbation of the naturally occurring processes [15]. Kaur and co-workers [16] demonstrated a convenient and efficient synthesis of new triazole β-lactam conjugates using click chemistry. Their method involves the propargylation of β-lactam, followed by Cu-catalyzed click reaction cycloaddition strategy at N-1 with aryl azides to afford 1,2,3-triazole conjugates (Scheme 3).


Scheme 3

Cycloadditions of copper(I) acetylides to azides and nitrile oxides provide ready access to 1,4-disubstituted 1,2,3-triazoles. For instance, Himo and co-workers [17] successfully employed 1,3,-dipolar cycloaddition reaction between terminal alkyne and an organic azide in the presence of $CuSO_4.5H_2O$/sodium ascarbate in water and few drops of t-butyl alcohol at room temperature to obtaine disubstituted 1,2,3-triazoles. The process is highly reliable and exhibits an unusually wide scope with respect to both components. Computational studies revealed a nonconcerted mechanism involving unprecedented metallacycle intermediates. Kim and co-workers [18] developed the Cp_2Ni/Xantphos catalytic system, that enables the synthesis of 1,5-disubstituted 1,2,3-triazoles under aqueous and ambient conditions (Scheme 4). This method is found simple and scalable with a broad substrate scope including both aliphatic and aromatic substrates.


Scheme 4
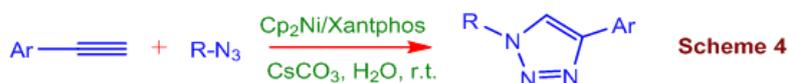
Smith *et al* [19] developed a mild, zinc-mediated method for regioselective formation of 1,5-substituted 1,2,3-triazoles from a wide range of azides and alkynes in the presence of diethylzinc and N-methylimidazole in THF at room temperature. The triazole 4-position was further functionalized by reaction of the intermediate aryl-zinc with various electrophiles to accommodate a diverse three-component coupling strategy. A ruthenium-catalyzed cycloaddition of *N*-Boc ynamides with azides gives protected 5-amino-1,2,3-triazole-4-carboxylic acids, which are suitable for the preparation of peptidomimetics. When aryl or alkyl azides are reacted with *N*-Boc-aminopropiolates or arylynamides, the cycloaddition occurs with complete regiocontrol, while *N*-Boc-alkyl ynamides yields a mixture of regio-isomers (Scheme 5) [20].


Scheme 5
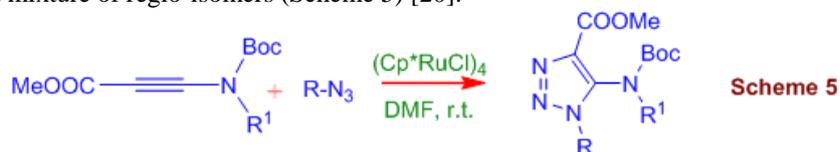
Alkynes undergo 1,3-dipolar cycloaddition with nitrile oxides [21], nitrile imine [22] and azides to form isoxazoles, pyrazoles, and triazoles respectively. Kwok and co-workers [23] synthesized 1,5-diarylsubstituted 1,2,3-triazoles in high yields from aryl azides and terminal alkynes in DMSO in the presence of a catalytic amount of tetraalkylammonium hydroxide or *t*-BuOK for base-labile substrates. Their reaction is simple, does not require a transition-metal catalyst, and is not sensitive to atmospheric oxygen and moisture. The use of *t*-BuOK in wet DMF as desilylating reagent in a cycloaddition reaction of aromatic azides and trimethylsilyl alkynes was developed by Wu *et al* [24] to obtain 1,5-disubstituted 1,2,3-triazoles regioselectively in good yields at ambient temperature (Scheme 6).

Scheme 6
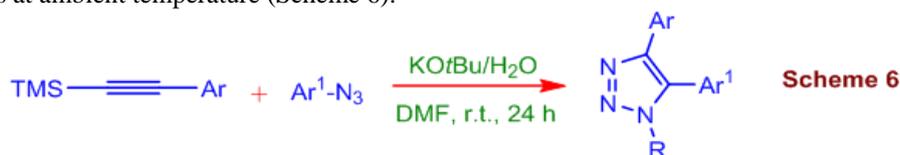
In the presence Cp*RuCl(PPh$_3$)$_2$ as catalyst, primary and secondary azides react with a broad range of terminal alkynes containing a range of functionalities selectively producing 1,5-disubstituted 1,2,3-triazoles. The study reports that both complexes also promote the cycloaddition reactions of organic azides with internal alkynes, providing access to fully-substituted 1,2,3-triazoles [25]. Wei and coworkers [26] reported that a Cu/Pd transmetalation relay catalysis enables a three-component click reaction of azide, alkyne, and aryl halide to produce 1,4,5-trisubstituted 1,2,3-triazoles in one step with complete regioselectivity (Scheme 7). This reaction offers an alternative to the well-established CuAAC click reactions only working on terminal alkynes.

Scheme 7
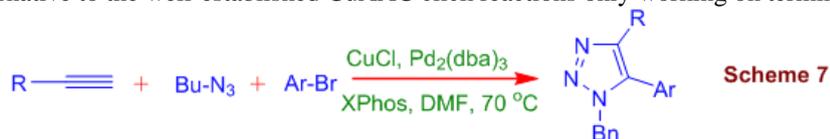
The use of inexpensive copper catalysts enabled modular one-pot multicomponent syntheses of fully decorated triazoles through a sustainable "click" reaction/direct arylation sequence was reported by Ackermann *et al* [27]. Wu and co-workers [28] developed a method for the regiospecific synthesis of 1,4,5-trisubstituted-1,2,3-triazole catalyzed by copper(I) iodide, involves 1,3-dipolar cycloaddition of an azide to terminal alkyne in the presence of CuI-ICl /Et$_3$N in THF as solvent. Yan *et al* [29] reported the copper(I)-catalyzed three-component reaction of amines, propargyl halides and azides to form 1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines in water. The advantages of the method are high atom economy, low environmental impact, atmospheric oxygen, wide substrate scope, mild reaction condition and good yields. Wang and co-workers [30] developed Copper(I)-catalyzed three-component one pot synthesis of 5-alkynyl-1,2,3-triazoles via click alkynylation (Scheme 8).


Scheme 8
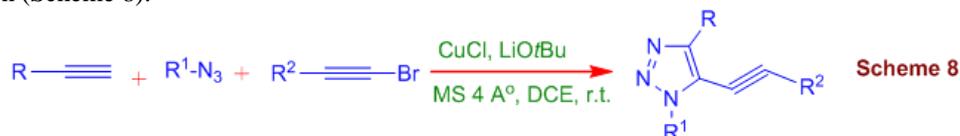
2.2 From alkynes and aryl/alkyl halides

Self-assembly of copper sulfate and a poly(imidazole-acrylamide) amphiphile provides a highly active, reusable, globular, solid-phase catalyst for click chemistry. In view of this, Yamada and co-workers [31] developed an insoluble amphiphilic polymeric imidazole Cu catalyst for the cycloaddition of various alkynes and organic azides at very low catalyst loadings without loss of activity to obtain the triazoles quantitatively. A tandem catalysis protocol based on decarboxylative coupling of alkynoic acids and 1,3-dipolar cycloaddition of azides avoids usage of gaseous or highly volatile terminal alkynes, reduces handling of potentially unstable and explosive azides to a minimum, and furnishes various functionalized 1,2,3-triazoles with high purity. Kolarovic *et al* [32] demonstrated the synthesis of disubstituted 1,2,3-triazoles by the reaction of alkyl/aryl iodide and alkynyl carboxylic acid, and sodium azide in the presence of L-proline, $CuSO_4$, sodium ascorbate and K_2CO_3 in DMSO-water solvent (Scheme 9)

A well-defined copper(I) isonitrile complex is an efficient, heterogeneous catalyst for azide-alkyne cycloadditions and three-component reactions of halides, sodium azide and alkynes to form 1,4-disubstituted 1,2,3-triazoles in high yields under mild conditions in water. The complex can be recycled for at least five runs without significant loss of activity by simple precipitation and filtration [33]. Lal and co-workers [34] developed a true click catalytic system is based on commercially available [$CuBr(PPh_3)_3$]. It was observed that the system is active at room temperature, with catalyst loadings less than 0.5 mol %, in the absence of any additive, and it does not require any purification step to isolate pure triazoles (Scheme 10).
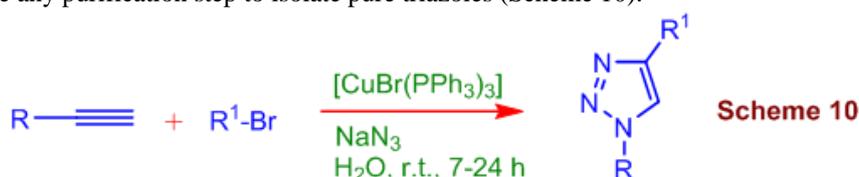

2.3 From alkenes and an organic azide

Alkenes are considered as important precursor for the synthesis of several classes of bioactive compounds in synthetic and bioorganic chemistry. For instance, they have been extensively used in the construction of aziridines [35], cyclopropanes [36, 37], pyrrolines [38], benzothiazepines, [39, 40], piperidones [41, 42] and triazoles. Thomas *et al* [43] developed a general and regioselective metal-free cycloaddition of organic azides to a hitherto underexplored bromovinylsulfonyl fluoride building block provides 4-fluorosulfonyl 1,2,3-triazoles (Scheme 11). The reaction was found efficient for the synthesis of various sulfonates, sulfonamides, and sulfonic acid derivatives of triazoles.

1,2,3-Triazoles were prepared in good yields by cycloaddition of alkyl azides onto enol ethers under solventless conditions. The reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions and is easily scalable [44]. Banday and co-workers [45] reported the regioselective one-pot synthesis of 1,5-disubstituted 1,2,3-triazoles through N/C-heterocyclization of allenylindium bromide across aryl azides in a sequential route in the presence of butylamine as base in THF-H_2O medium at room temperature. Yang and co-workers [46] reported the synthesis of 4-acyl-*NH*-1,2,3-triazoles with high efficiency through the cycloaddition reactions between *N,N*-dimethylenaminones and tosyl azide. The method has featured with extraordinary sustainability in water as the sole medium, and is free of any catalyst or additive, authentically mild conditions as well as practical scalability (Scheme 12).
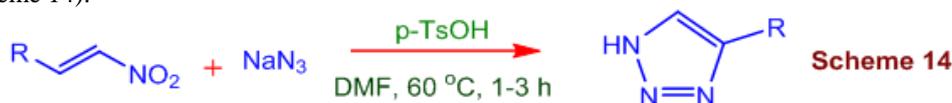
Scheme 12

Wang and co-workers [47] reported the Ce(OTf)$_3$-catalyzed [3+2] cycloaddition of organic azides with nitroolefins and subsequent elimination reaction selectively produces 1,5-disubstituted 1,2,3-triazoles. It was observed that both benzyl and phenyl azides react with a broad range of aryl nitroolefins with wide range of functionalities. Chen *et al* [48] demonstrated that a copper-catalyzed [3+2] cycloaddition/oxidation reaction of nitro-olefins with organic azides affords a broad range of 1,4-(-NO$_2$),5-trisubstituted 1,2,3-triazoles with high regioselectivities without elimination of HNO$_2$ (Scheme 13).

Scheme 13
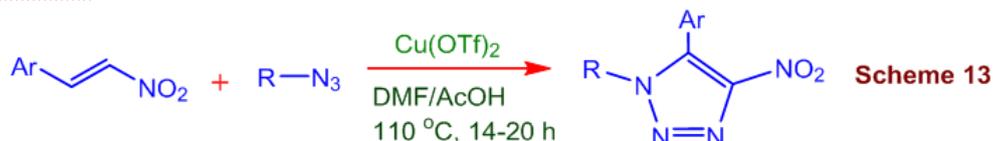
2.4 From alkenes and sodium azide

Barluenga and co-workers [49] reported palladium catalysed cycloaddition reaction of alkenyl bromide and sodium azide at 110 ^{o}C. They were showed that the Pd-catalyzed synthesis of 1*H*-triazoles, which involve the reaction of alkenyl halides and sodium azide in the presence of Pd$_2$dba$_2$-xantphos in dioxane. The protocol represents a completely new reactivity pattern in the context of Pd chemistry. Quan *et al* [50] proved that the *p*-TsOH is a vital additive in the 1,3-dipolar cycloaddition of nitroolefins and sodium azide. The study shows that the *p*-TsOH-mediated cycloaddition enables a rapid synthesis of valuable 4-aryl-*NH*-1,2,3-triazoles in high yields (Scheme 14).


Scheme 14

Zhang and co-workers (51) developed a highly efficient and effective protocol for the synthesis of *N*-unsubstituted 4-aryl-1,2,3-triazoles is promoted by Amberlyst-15 (Scheme 15). The study shows that an ion exchange resin can be recycled and reused up to eight times without loss of catalytic activity. Apart from their utility as useful scaffolds, alkenes are also used as synthons in the synthesis of biologically important compounds like isoxazoles [52, 53], pyrazoles [54, 55], oxadiazoles [56, 57], and thiadiazoles [58, 59] etc.


Scheme 15

2.5 From carbonyl compounds

Luvino and co-workers [60] developed a reliable and operationally simple one-pot reaction for a one-carbon homologation of various aldehydes followed by Cu-catalyzed azide-alkyne click chemistry to obtain 1,4-disubstituted 1,2,3-triazoles in good yields without the need for isolation of the alkyne intermediates. Wu *et al* [61] demonstrated the mild and metal-free multi-component reaction that enables the synthesis of 4,5-disubstituted 1*H*-1,2,3-triazoles from phosphonium salts, aldehydes, and sodium azide (Scheme 16). An organo catalyzed coupling of the formyl group with the phosphonium group provides an olefinic phosphonium salt as key intermediate, which undergoes [3+2] cycloaddition with the azide.


Scheme 16
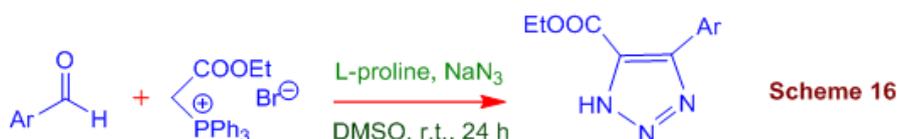
A copper-catalyzed three-component reaction of methyl ketones, organic azides, and DMF as one-carbon (C1) donor provides 4-acyl-1,2,3-triazoles in good yields. The transformation proceeds via an oxidative C-H/C-H cross-dehydrogenative coupling followed by an oxidative 1,3-dipolar cycloaddition [62, 63]. Shastin and co-workers [64] demonstrated that the reaction of 4,4-dichloro-1,2-diazabuta-1,3-dienes with sodium azide provides extremely rare 1,1-bisazides. These highly unstable compounds are prone to eliminate N_2 to cyclize into 4-azido-1,2,3-triazoles bearing two aryl groups at positions 2 and 5. This reaction enables a highly efficient synthesis of various 4-azidotriazoles.


Scheme 17
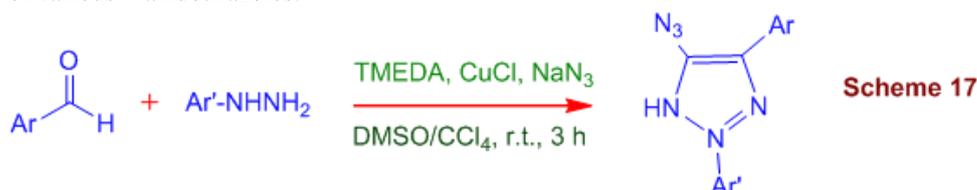
2.6 Other important methods

The synthesis of 1-monosubstituted aryl 1,2,3-triazoles was achieved in good yields using calcium carbide as a source of acetylene. The copper-catalyzed 1,3-dipolar cycloaddition reactions were carried out without nitrogen protection and in a MeCN-H_2O mixture (Scheme 18) [65].

Scheme 18
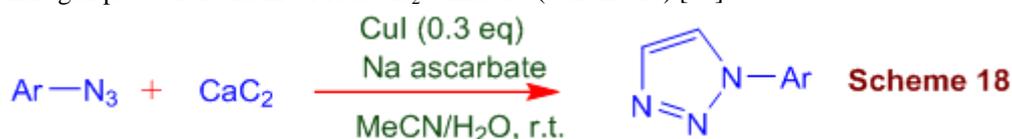
Metallo-β-lactamases (MBLs) are an emerging cause of bacterial antibiotic resistance by hydrolysing all classes of β-lactams except monobactams, and the MBLs are not inhibited by clinically available serine-β-lactamase inhibitors. Muhammada and co-workers [66] prepared the series of *N*H-1,2,3-triazoles through Banert cascade reaction as the key step (Scheme 19). They were evaluated the prepared compounds for their inhibitor properties against the MBLs VIM-2, NDM-1 and GIM-1, and VIM-2; the results showed IC50 values down to nanomolar range. The inhibitors show reduced MIC in synergy assays with *P. aeruginosa* and *E. coli* strains harbouring VIM enzymes.


Scheme 19
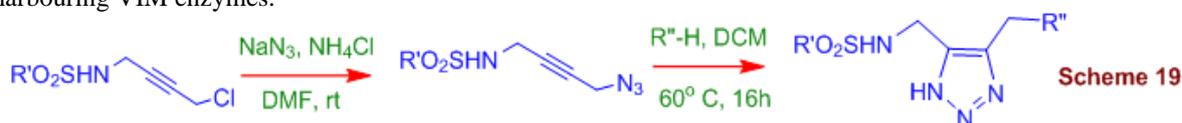
Electrolytic copper is a well-known form of pure, oxygen free copper that is used for industrial applications. Mularski and co-workers [67] reported the utility of electrolytic copper as effective catalytic system for the synthesis of 1,2,3-triazoles. The addition of less than 0.015 mol equivalent of copper powder effectively catalyzed the one-pot synthesis of triazoles from a diverse range of organic halides, alkynes, and sodium azide (Scheme 20). Quantitative conversions in aqueous solvents can be achieved within minutes, and the heterogenous catalyst afforded a low level of copper contamination in the products, thus meeting the rigorous criteria of the pharmaceutical industry.


Scheme 20
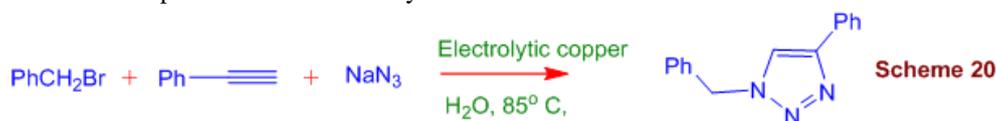
Kafle and co-workers [68] attempted to prepare azido-substituted aurones via a copper-catalyzed azidation, surprisingly they obtained triazole derivatives instead of the desired products. The reaction was unusual and they observed that copper was not required for this reaction, but simply thermal treatment with sodium azide in a polar aprotic solvent (Scheme 21). Regardless, the potential utility of these easily accessible, multifunctional compounds should engender further interest and applications.

Scheme 21

Wan and co-workers [69] reported the three-component reactions of enaminones, tosylhydrazine and primary amines in the presence of molecular iodine and absence of metal hydride that enabled a regioselective construction of 1,5-disubstituted 1,2,3-triazoles via cascade dual C-N bond formation, N-N bond formation and an acyl migration-based C-C bond formation. They were also reported the Domino reactions between NH-based secondary enaminones and tosyl azide enable the synthesis of various *N*-substituted 1,2,3-triazoles via a key Regitz diazo-transfer process by employing *t*-BuONa as the base promoter (Scheme 22) [70]. The reactions proceed efficiently at room temperature with good substrate tolerance.


Scheme 22
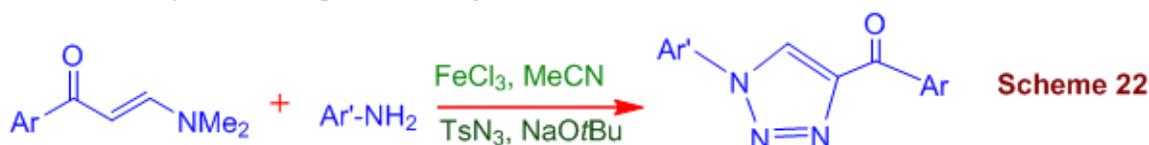
Microwave irradiation significantly enhances the rate of formation of 1,4-disubstituted 1,2,3-triazoles from alkynes and in situ generated azides. Azides are derived from an efficient one-pot azidation of anilines with the reagent combination *t*-BuONO and TMSN$_3$ [71]. Liu and co-workers [72] prepared triazole-based monophosphine ligands via efficient cycloadditions. Palladium complexes derived from these ligands are highly active catalysts for Suzuki-Miyaura coupling and amination reactions of aryl chlorides. Cai *et al* [73] developed an efficient I$_2$/TBPB mediated oxidative formal [4+1] cycloaddition of *N*-tosylhydrazones with anilines (Scheme 23), the protocol represents a simple, general, and efficient approach for the construction of 1,2,3-triazoles under metal-free and azide-free conditions.

Scheme 23
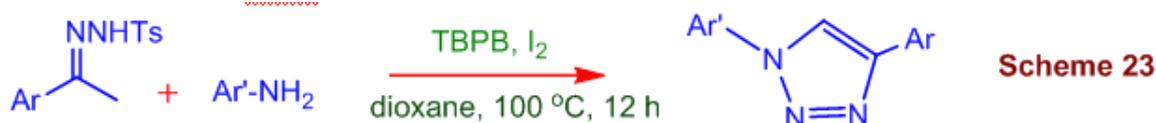
Triazoles have been synthesized via a three-component coupling reaction of unactivated terminal alkynes, allyl carbonate, and trimethylsiyl azide under Pd(0)-Cu(I) bimetallic catalysis [74]. Amantini and co-workers [75] reported the TBAF-catalyzed [3+2] cycloadditions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with TMSN$_3$ under solvent free conditions leads to 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1*H*-1,2,3-triazoles under mild reaction conditions with good to excellent yields. A palladium-catalyzed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide in one pot enables an efficient synthesis of 4,5-disubstituted-1,2,3-(NH)-triazoles in excellent yields [76]. Taylor and co-workers [77] demonstrated that the phenyl esters of α-azido acids react with trialkylphosphines in THF/H$_2$O to give 5-substituted 2*H*-1,2,3-triazol-4-ols (Scheme 24), whereas their reaction with PPh$_3$ provides amino esters as the major product and no triazoles.

Scheme 24

Jiang and co-workers [78] synthesized 4-Aryl-1*H*-1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids and sodium azide by using inexpensive copper(I) iodide as the catalyst in the presence of cesium carbonate as base and DMSO as solvent. 4-Aryl-1*H*-1,2,3-triazoles were synthesized from *anti*-3-aryl-2,3-dibromopropanoic acids and sodium azide by a one-pot method using *N,N*-dimethylformamide as solvent in the presence of Pd$_2$(dba)$_3$ and Xantphos [79]. Chen *et al* [80] proved that in the presence of inexpensive copper (I) iodide as the catalyst, a series of 1,4-disubstituted 1,2,3-triazoles were synthesized in a one-pot process from *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides in dimethyl sulfoxide (Scheme 25).

Scheme 25
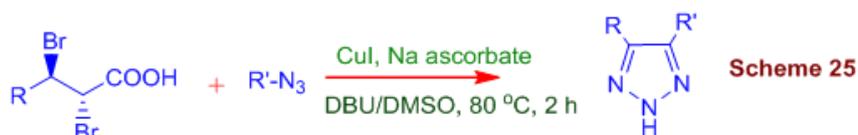
III. 1,2,3-Triazole-Heterocycle Molecular Hybrids

It was interesting to observe that, the compounds with two or more pharmacaphoric moieties possess enhanced biological activities. In this context a lot of attempts have been made to incorporate a other pharmacaphore to the parent 1,2,3-triazole system, and study the combined biological potencies. Reaction of 4-bromo-*NH*-1,2,3-triazoles with alkyl halides in the presence of K_2CO_3 in DMF produced the corresponding 2-substituted 4-bromo-1,2,3-triazoles in a regioselective process. Subsequent Suzuki cross-coupling reaction provided an efficient synthesis of 2,4,5-trisubstituted triazoles, whereas hydrogenation furnished an efficient synthesis of 2,4-disubstituted triazoles [81]. Recently Liu and co-workers [82] developed a efficient route for synthesis of 1-benzyl-5-aryl-1,2,3-triazoles by regioselective direct arylation between 1-benzyl-1,2,3-triazole and Ar-Br in the presence of $Pd(OAc)_2$ as catalyst under microwave assisted reaction conditions. It was observed that the reaction proceeded smoothly with high chemoselectvity at C5 position with good yields (Scheme 26).

Scheme 26

Trifluoromethylated triazoles can make favourable changes in "drug-like" molecules. In this view, Panja *et al* [83] reported a new method for the trifluoromethylation of 1-aryl-4-iodo-1,2,3-triazoles, which involves CuI-mediated reaction using methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA). Interestingly, it was observed that the presence of the tetrabutylammonium iodide, (TBAI) as PTC enhanced conversion reaction in multi gram scale and has broad functional group tolerance (Scheme 27).

Scheme 27
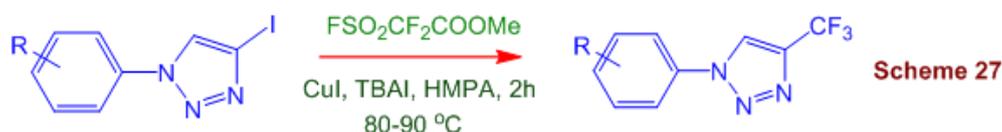
A catalyst-free and regioselective N arylation enables the synthesis of N^2-aryl-1,2,3-triazoles in the presence of sodium carbonate in toluene at 100 ^{o}C in very good yields. The method described by Roshandel *et al* [84] was scalable postmodification protocol is effective for a wide range of substrates. Li *et al* [85] developed a new method for the preparation of N^1- and N^2-indol-3-yl 1,2,3-trizole products through gold catalyzed cascade reaction of *o*-alkynyl arylazides with benzo-1,2,3-triazoles (Scheme 28), in which, the *in situ* generated α-imino gold carbene intermediate was intercepted by various types of triazole compounds. N^1-selective nucleophilic attack was favored to give moderate to high N^1/N^2 selectivity.


Scheme 28

N_3-Alkylation of 1-(pivaloyloxymethyl)-1,2,3-triazoles with alkyl triflates, followed by a nucleophile-promoted N1-dealkylation of the resulting strongly electrophilic intermediate triazolium salts, provides 1,5-disubstituted 1,2,3-triazoles [86]. Ren and co-workers [87] reported that the palladium acetate/$K_2S_2O_8$ facilitates regioselective alkoxylation of *ortho*- C–H bonds at C(4)-aryl of 1,4-disubstituted 1,2,3-triazoles in good yields

under the directing of the triazole ring (Scheme 29). The alkoxylated triazoles exhibit strong antifungal potential to fight against root-rot disease of *Panax notoginseng*.

Scheme 29

Palladium catalyzed orthogonal arylation reaction sequences lead to diversely substituted 1,2,4-triazoles. Azzouni *et al* [88] reported the preparation of 1,3,5-trisubstituted 1,2,4-triazoles using selective orthogonal arylation reaction sequences. It was observed that, the ligand free Pd-catalyzed arylation allowed incorporation of various (het)aryl units exclusively at the vinyl fragment of N1 substituted or N1-H precursors, and double arylations starting from *ortho*, *meta* and *para* bisiodobenzenes led to extended bistriazolyl derivatives. In contrast, Cu-catalyzed arylation using the ligand pyridylmethylamine led to N1-arylated triazoles keeping intact the vinyl moiety (Scheme 30). Arylation process was compatible with electron donating groups in *ortho*, *meta* and *para* positions and tolerated electron withdrawing groups with a lesser extent.

Scheme 30
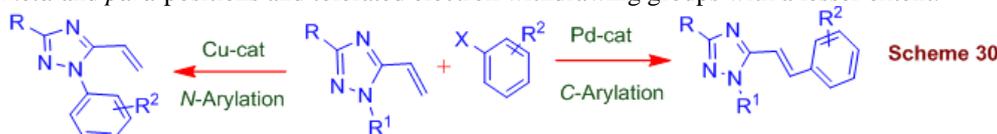
Chuprakov and coworkers [89] demonstrated a highly efficient method for the synthesis of multisubstituted 1,2,3-triazoles via a direct Pd-catalyzed C-5 arylation. The method involve the reaction of disubstituted 1,2,3-triazole with aryl bromide in the presence of palladium acetate and Bu4NOAc in NMP at 100 ^{o}C. Ackermann *et al* [90] extended the same reaction by the use of nontoxic polyethylene glycol (PEG) as solvent and MesCO$_2$H as cocatalyst enabled user-friendly palladium(0)-catalyzed C-H bond functionalizations under air in the absence of phosphine ligands. The method is better suited for the direct arylations of 1,2,3-triazoles, and recycling of the catalytic system led to a slight decrease of activity. Liegault and coworkers [91] extensively studied the conditions for the palladium-catalyzed direct arylation of a wide range of heterocycles with aryl bromides employ a stoichiometric ratio of both coupling partners, as well as a substoichiometric quantity of pivalic acid, which results in significantly faster reactions (Scheme 31). They were also studied the influence of the nature of the aryl halide on arylation reactions.


Scheme 31
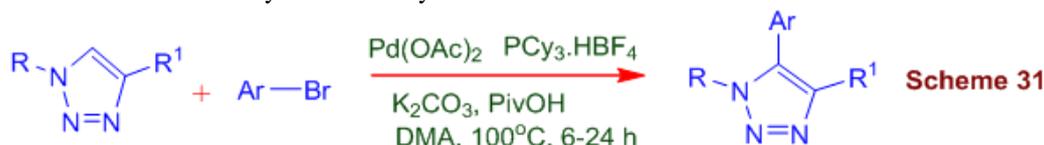
IV. Biological Applications
4.1 Antimicrobial activity

Thanh and co-workers [92] synthesized the series of 2-amino-7-propargyloxy-4*H*-chromene-3-carbonitriles from 2-amino-7-phydroxy-4*H*-chromene-3-carbonitriles and propargyl bromide in K$_2$CO$_3$/acetone and NaH/DMF. Then they transformed them in to 1*H*-1,2,3-triazole-4H-chromene−D-glucose conjugates of propargyl ethers and tetra-*O*-acetyl-β-D-glucopyranosyl azide, using optimal catalyst Cu–MOF-5 (Scheme 32). The results indicated that all compounds exhibit antimicrobial activities (MIC's of 1.56–6.25 μM).

Scheme 32

Subhashini and co-workers [93] described the click followed by multi-component reaction for the synthesis of a new class of antimicrobial and antioxidants, imidazole linked 1,2,3-triazole hybrids (**1**) and imidazole linked bis-triazole derivatives (**2**). The reactions were carried out by two different techniques, conventional heating and microwave irradiation. Microwave irradiation method offers excellent yields, lesser reaction times and environmental friendly reactions. The results of the study indicated that some target

compounds exhibited promising antimicrobial potency against gram-positive, gram-negative strains, and also excellent antioxidant activity. Nejadshafiee *et al* [94] reported the use of copper imprinted periodic mesoporous organosilica nanocomposite (Cu/PMO NC) as catalyst for the preparation of *β*-hydroxy-1,2,3-triazoles derivatives. The method involves the multicomponent reaction between epoxides, terminal alkyne and sodium azide in aqueous media using click chemistry.
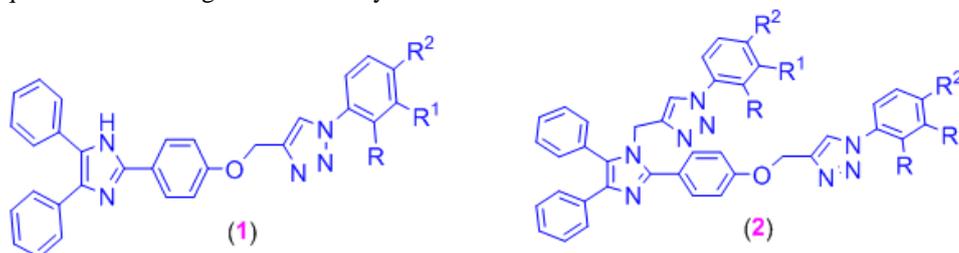
Dubovis and co-workers [95] developed a protocol, involves the deoxygenation reaction of 1-(1-*tert*-butyl-3-nitroazetidine-3-yl)-1*H*-1,2,3-triazoles for the synthesis of substituted 1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles (**3**) and reported that the synthesized compounds exhibit fungicidal activity against wide range of phytopathogenic fungi. Reddyrajula *et al* [96] extensively studied antitubercular activity of phenothiazine-1,2,3-triazole molecular hybrids (**4**, **5**). They were evaluated these compounds for *in vitro* growth inhibition activity against Mycobacterium tuberculosis H37Rv strain. The investigation result shows that most of the compounds exhibited significant activity with MIC value 1.6 µg/mL, which is two-fold higher than the MIC value of standard first-line TB drug pyrazinamide, and all compounds are proved to be non-toxic against VERO cell lines.
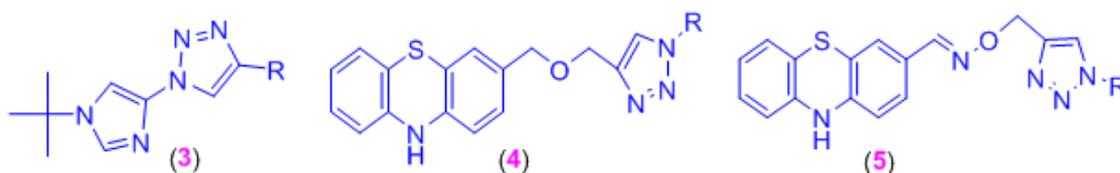
Khanapurmaath and co-workers [97] prepared cyclic ureido based mono/*bis*-coumarin 'click triazoles' by the reaction of 4-(azidomethyl)-2*H*-chromen-2-ones/quinolin-2(1*H*)-ones and propargyl ethers and evaluated for their anti-tuberculosis activities. The results show that the synthesized triazoles inhibited *M. tuberculosis H37Rv*. Interestingly, it was observed that benzimidazolono-bis-coumarinyl triazoles exhibited greater, while theophylline/uracil-based mono/*bis*-coumarin triazoles lesser inhibition against *M. tuberculosis H37Rv*. The designed series of urea-1,2,3-triazole-amide hybrids of urea derivatives show antibacterial and antifungal susceptibilities [98]. Nalawade and co-workers [99] reported the synthesis of 1-substituted benzyl-4-[1-phenyl-3-(4-methyl-2-aryl-1,3-thiazol-5-yl)-1*H*-pyrazol-4-yl]-1*H*-1,2,3-triazoles by click reaction of 5-(4-ethynyl-1-phenyl-1*H*-pyrazol-3-yl)-4-methyl-2-aryl-1,3-thiazole with benzyl azide (Scheme 33). The report says that all thiazolyl-pyrazolyl-1,2,3-triazoles possess an antibacterial activity against *E. coli*, *P. mirabilis*, *S. albus*. Further, some compounds shows ergosterol inhibition against *A. niger* cells sample at 31.5 µg/mL concentration.

Sun and co-workers [100] showed that 4-phenyl-1*H*-1,2,3-triazole phenylalanine derivatives acts as HIV-1 CA inhibitors. Their study involves the synthesis, and evaluation as HIV-1 CA inhibitors, and reveal that most compounds of the series possess potent antiviral activities, the anti-HIV-1 activity of (**6**) (EC$_{50}$ = 3.13 µM) is particularly prominent. The mechanism of action displays the effects in both the early and late stages of HIV-1 replication. Santhosh Kumar *et al* [101] developed a continuous-flow synthetic protocol for the synthesis of 1,2,3-triazole-furan hybrid chalcone derivatives, their method involves the base catalyzed Claisen-Schmidt condensation of 1-phenyl-1*H*-1,2,3-triazole-4-carbaldehydes with 2-acetylfuran. The synthesized compounds showed promising antimicrobial activities.

(6)

## 4.2 Anticancer, Anti-proliferative and Anti-inflammatory activity

Cancer is a multifactorial disorder involving multiplicity of interrelated signaling pathways and molecular targets. To overcome this, Elzahhar and co-workers [102] 1,2,3-triazoles hybridized with some pharmacophoric anticancer fragments, which acts as simultaneous inhibitors of COX-2, 15-LOX and tumor associated carbonic anhydrase enzymes. Their investigatation result shows that compounds (**7**) and (**8**) were potent inhibitors of COX-2 and 15-LOX enzymes. COX-2 inhibitory activity was demonstrated by the inhibition of the accumulation of 6-keto-PGF1α in two cancer cell lines. The strong to moderate inhibitory activities were observed in the *in vitro* anti-proliferative assay on lung (A549), liver (HepG2) and breast (MCF7) cancer cell lines (IC$_{50}$ 2.37–28.5 μM). In light of these data, these compounds could offer new structural insights into the understanding and development of multi-target COX-2/15-LOX/hCA inhibitors for anticancer outcomes.
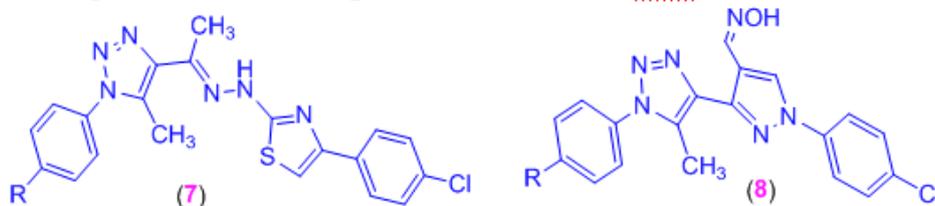
Gholampour *et al* [103] prepared 1,4-naphthoquinone-1,2,3-triazole hybrids through click reaction of 2-(prop-2-ynylamino)naphthalene-1,4-dione and different azidomethyl-benzene derivatives, and assessed for their anticancer activity against cancer cell lines (MCF-7, HT-29 and MOLT-4) by MTT assay. The result shows that amongst the series, compound (**9**) bearing 4-trifluoromethyl-benzyl demonstrated good cytotoxic potential and highest activity against tested cell lines, Flow cytometric analysis revealed that compounds arrested cell cycle at G0/G1 phase in MCF-7 cells. Therefore, these aminonaphthoquinone-1,2,3-triazoles could be promising molecules as anticancer agents. Ashour *et al* [104] proved that 1,2,3-triazole-chalcone hybrids possesses promising anticancer activities, in particular compound (**10**) having 3, 4-dimethoxyphenyl chalcone moiety found most potent, which inhibited the growth of RPMI-8226 and SR leukemia cell lines by 99.73% and 94.95% at 10 μM, respectively. It also inhibited the growth of M14 melanoma, K-562 leukemia, and MCF7 breast cancer cell lines by more than 80% than methotrexate with IC$_{50}$ values less than 1 μM and high selectivity index reached to 104 fold on MCF7.
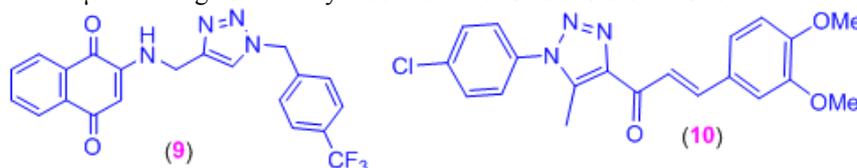

The suboptimal therapeutic responses along with the side effect profile associated with the existing anticancer therapy have necessitated the development of new therapeutic modalities to curb this disease. In this context, Khan and co-workers [105] reported that 1,2,3-triazole linked 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylates possess anticancer potential against four human cancer cell lines- MCF-7 (breast), A549 (Lung) and HCT-116 and HT-29 (Colon). Results indicate that compounds showed promising growth inhibition against all the cell lines. Among them, compound (**11**) displayed IC$_{50}$ values of 1.962, 3.597, 1.764 and 4.496 μM against A549, HCT-116, MCF-7 and HT-29 cell lines respectively. Boshra *et al* [106] devised a hybrid pharmacophore approach to design a series of isatin analogues of 2′-hydroxychalcone-triazole hybrids (**12**), and their anti-inflammatory activity studies of these compounds shows that, they were selective inhibitors for COX-2 (IC$_{50}$ = 0.037–0.041 μM) and 15-LOX (IC$_{50}$ = 1.41–1.80 μM). Some compounds showed 116%, 113% and 109% of the *in vivo* anti-inflammatory activity of celecoxib. Therefore, these compounds are potent dual inhibitors of COX-2 and 15-LOX.
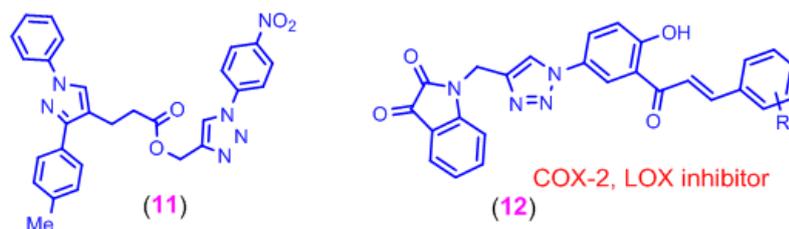
Click chemistry tool was employed for the synthesis of 1,2,3-triazole-benzimidazole-chalcone heterocyclic hybrids between different azide derivatives and substituted benzimidazole terminal alkynes bearing a chalcone moiety by Djemoui *et al* [107]. The study reveals that, these hybrids have the anti-proliferative potential in breast and prostate cancer cell lines. Particularly, the compounds having the chloro substituents at the chalcone ring of the triazole-benzimidazole-chalcone core enhanced the cytotoxic effects, and the benzyl group linked to the 1,2,3-triazole moiety provides more antiproliferative potential. Pokhodylo *et al* [108] prepared 1,2,3 triazole derivatives and evaluated for their *in vitro* antitumor activity against NCI60 cell lines. The result shows that some compounds showed slight anticancer activity.

Madasu and co-workers [109] synthesized a series of novel myrrhanone B based 1,2,3-triazole hybrids by employing regioselective CuAAA reaction in highly efficient manner. They were extensively studied for their biological potencies such as antiproliferative, anti-inflammatory and anti-diabetic activities. Naouri *et al* [110] reported the regioselective synthesis of 1,2,3-triazole-acridinedione/xanthenedione heterocyclic hybrids via 1,3-dipolar coupling reaction of *N*-substituted-acridinedione-alkyne substrates with various aromatic azides. The synthesized triazole hybrids displayed cytotoxic activity on two human breast cancer cell lines (MDA-MB-231, T47-D) and one prostate cancer cell line (PC3), and the most active being *O*-1,2,3-triazole-xanthenedione hybrid with $IC_{50} \leq 20\,\mu M$ in breast cancer and $IC_{50} = 10\,\mu M$ in prostate cancer cell lines. Djemoui and coworkers [111] synthesized a series of triazole-benzimidazole-chalcone derivatives from azide derivatives and substituted benzimidazole terminal alkynes bearing a chalcone moiety, and these compounds show anti-proliferative potential in breast and prostate cancer cell lines. The results indicated that the presence of chloro substituents at the chalcone ring of the triazole-benzimidazole-chalcone skeleton enhanced the cytotoxic effects. The benzyl group linked to the 1,2,3-triazole moiety provides more antiproliferative potential.

Sayeed and co-workers [112] reported that imidazopyridine linked triazole hybrid conjugates possess cytotoxicity against human lung (A549), human prostate (DU-145), human colon (HCT-116) and breast (MDA-MB 231) cancer cell lines. Amongst, the series the conjugate (**13**) showed significant antitumor activity against A549 with IC_{50} values of 0.51 µM. Flow cytometry analysis revealed that these conjugates arrested the cell cycle at G_2/M phase in human lung cancer cell line (A549). Li and co-workers [113] synthesized homoerythrina alkaloid analogues bearing a triazole moiety as PARP-1 inhibitors. The result shows that, amongst the series, compound (**14**) possess excellent activity to inhibit proliferation of A549 cells ($IC_{50} = 1.89\,\mu M$), which was higher than harringtonine ($IC_{50} = 10.55\,\mu M$), pemetrexed ($IC_{50} = 3.39\,\mu M$), and rucaparib ($IC_{50} = 4.91\,\mu M$). Furthermore, the selectivity index of this compound was higher than rucaparib and pemetrexed for lung cancer cells. Flow cytometry analysis showed that it significantly arrested the cell cycle in the S phase, then induced apoptosis of A549 cells (apoptosis rate is 46%), which effectively inhibited cell proliferation. Chekir and co-workers [114] demonstrated the regioselective synthesis of 1,2,3-triazole linked coumarinopyrazole conjugates *via* the copper(i)-catalysed alkyne-azide cycloaddition. The study shows that compound (**15**) of the series has improved anticholinesterase, anti-5-lipoxygenase, anti-tyrosinase, and cytotoxic activities.
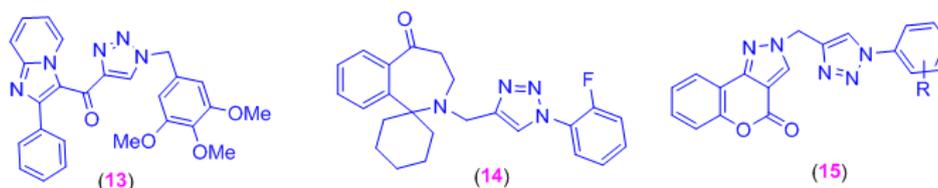
4.3 Anti-diabetic activity:

Diabetes is a non-communicable disease, which occurs either due to the lack of insulin or the inability of the human body to recognize it. The recent data indicates an increase in the trend of people diagnosed with Type 2 diabetes mellitus (T2DM). *α*-Glucosidase inhibitors are known to reduce the impact of carbohydrates on blood glucose level. Inhibiting the decomposition of carbohydrates into glucose or promoting glucose

conversion is considered to be an effective treatment for type 2 diabetes. Ye *et al* [115] designed a series of xanthone-triazole derivatives (**16**), and evaluated for their α-glucosidase inhibitory activities and glucose uptake in HepG2 cells. The results of their indicated that, most of the compounds showed better inhibitory activities than the parental compound (1,3-dihydroxyxanthone, $IC_{50} = 160.8\,\mu M$) and 1-deoxynojirimycin (control, $IC_{50} = 59.5\,\mu M$) towards α-glucosidase. The kinetics of enzyme inhibition showed that compounds were noncompetitive inhibitors, and molecular docking results were consistent with the noncompetitive property that these compounds bind to allosteric sites away from the active site. The glucose uptake results shows that compounds displayed high activities in promoting the glucose uptake, and most of these compounds were low-toxic to human normal hepatocyte cell line (LO2). These xanthone-triazole hybrids possess dual therapeutic effects of α-glucosidase inhibition and glucose uptake promotion, and therefore, they could be used as antidiabetic agents against type 2 diabetes. In search of *α*-glucosidase inhibitors, Avula *et al* [116] reported the synthesis of a series of (*R*)-4-fluorophenyl-1*H*-1,2,3-triazole derivatives (**17**) and evaluated for their *α*-glucosidase inhibitory activity *in vitro*. Their structure-activity relationship study shows that the presence of 1*H*-1,2,3-triazole ring in (*R*)-4-fluorophenyl-1*H*-1,2,3-triazole derivatives has remarkable contribution in the overall activity, and the study unravelled a new class of triazole derivatives with *α*-glucosidase inhibitory activity
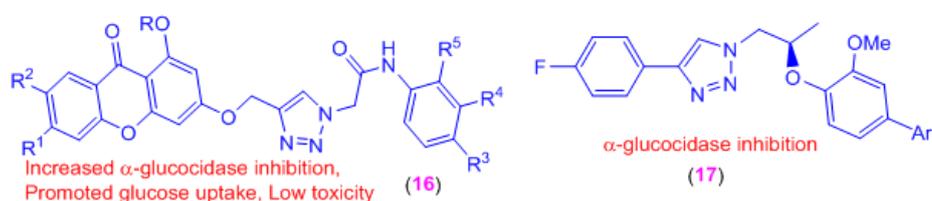
Asgari and co-workers [117] demonstrated that biscoumarin-1,2,3-triazole hybrids have α-glucosidase inhibitory potential. The results of their study reveal that, all compounds exhibited excellent α-glucosidase inhibitory activity with IC_{50} values of 13.0 ± 1.5 and $75.5 \pm 7.0\,\mu M$ comparable to acarbose ($IC_{50} = 750.0 \pm 12.0\,\mu M$). Compound of the series, (R^1=2-Cl, **18**) exhibited the highest inhibitory activity with ($IC_{50} = 13.0 \pm 1.5\,\mu M$) and was non-cytotoxic towards normal fibroblast cells. Saeedi *et al* [118] reported the synthesis and *α*-glucosidase inhibitory activity of quinazolinone-1,2,3-triazole hybrids. Their compounds exhibited good inhibitory activity against yeast *α*-glucosidase (IC_{50} 181.0–474.5 μM) even more potent than acarbose ($IC_{50} = 750.0$). Among them, compound (**19**) demonstrated the most potent inhibitory activity towards *α*-glucosidase. Furthermore, the binding modes of the most potent compound the *α*-glucosidase active site was studied through *in silico* docking studies. Also, lack of cytotoxicity of this compound was confirmed *via* MTT assay.
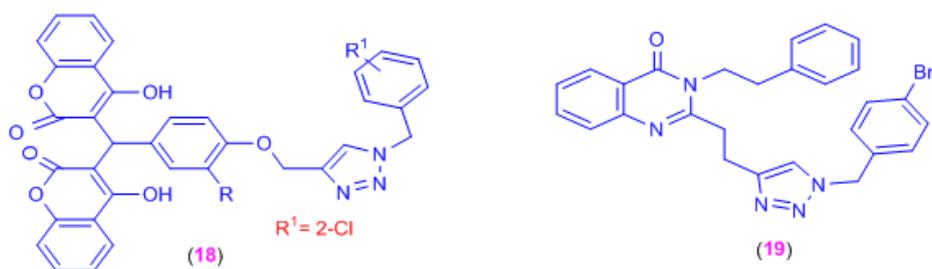

α-Glucosidase inhibitors hold great potential for the treatment of Type 2 diabetes mellitus. In this context, Asemanipoor and co-workers [119] synthesized benzimidazole-1,2,3-triazole hybrids (**20**) as new α-glucosidase inhibitors. The *in vitro* α-glucosidase inhibition results indicate that all compounds exhibited more inhibitory activity (IC_{50} values 25.2 ± 0.9-$176.5 \pm 6.7\,\mu M$) in comparison to standard acarbose ($IC_{50} = 750.0 \pm 12.5\,\mu M$). Saeedi and co-workers [120] did tedious work on the synthesis and α-glucosidase inhibitory activity of series of diarylimidazole-1,2,3-triazoles (**21**). Results reveals that all compounds are potent inhibitors of an enzyme α-glucosidase ($IC_{50} = 90.4$–246.7 μM) compared with the standard acarbose ($IC_{50} = 750.0\,\mu M$). Interestingly, compound 1-(3,5-dimethylbenzyl)-4-((4-(4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy)methyl)-1*H*-1,2,3-triazole of the series exhibited eight fold greater inhibition than the standard.
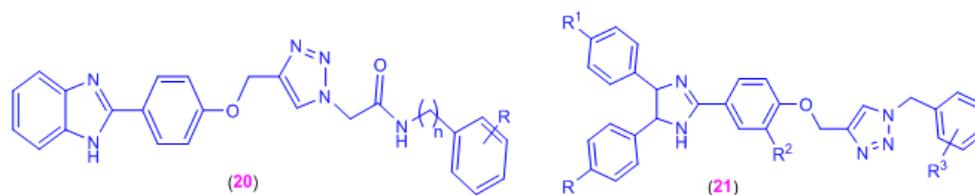
4.4 Other biological activities

Chamduang *et al* [122] reported the synthesis and aromatase inhibitory activities of triazole-tetrahydroisoquinolines. Their study revealed that, some compounds of the series, show significant aromatase inhibitory activity ($IC_{50} = 0.07–1.9$ μM). Interestingly, the analog bearing naphthalenyloxymethyl substituent at position 4 of the triazole ring (**22**) displayed the most potent aromatase inhibitory activity without significant cytotoxicity to a normal cell. Marques *et al* [123] extensively studied the series of *N*-1,2,3-triazole-isatin derivatives for multi-target activity which included cholinesterase (ChE) inhibition and β-amyloid (Aβ) peptide anti-aggregation properties. It was evident from the results that the compounds shows promisingly inhibit butyrylcholinesterase (BuChE), in particular against *equine* BuChE (*eq*BuChE) and *human* BuChE (*h*BuChE). Amongst, molecule (**23**) shows better inhibitions for *h*BuChE than *eq*BuChE. In addition, few of these compounds showed weak Aβ anti-aggregation activity. Hepatotoxicity and neurotoxicity studies shows that all compounds were non-hepatoxic and are only weakly neurotoxic.
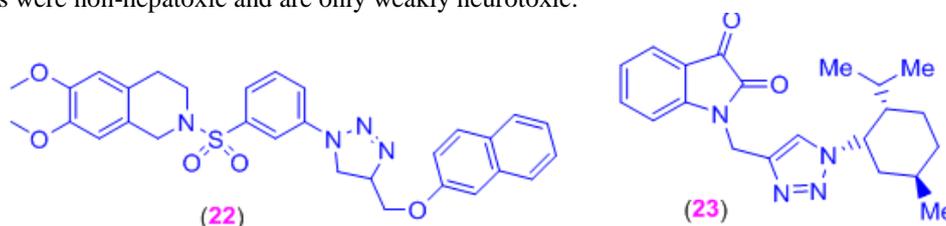

Macrophage migration inhibitory factor (MIF) is a versatile protein that plays a role in inflammation, autoimmune diseases and cancers. Development of novel inhibitors will enable further exploration of MIF as a drug target. Xiao and co-workers [124] synthesized indole-1,2,3-triazole conjugates (**24**), and investigated SAR of MIF inhibitors using a MIF tautomerase activity. It was observed from the results that transition metals such as copper (II) and zinc (II) interfere with the MIF tautomerase activity under the assay conditions. They explored EDTA buffer to avoid interference of residual heavy metals with tautomerase activity measurements. Giraudo *et al* [125] studied the bioisosteric application associated with hydroxy-1,2,3-triazole system (**25**). The results of a study devoted to obtain potential biomimetics of the γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (CNS).
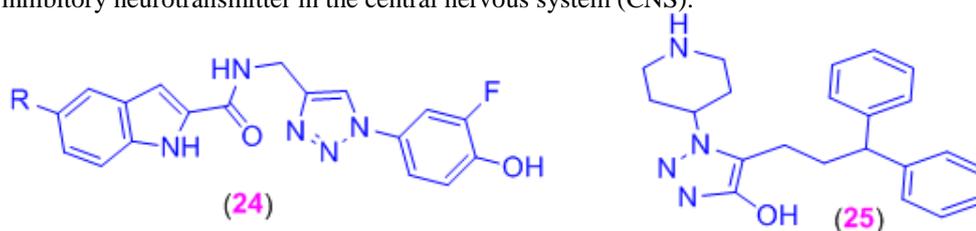

Peptidotriazolamers are hybrid foldamers with features of peptides and triazolamers, containing alternation of amide bonds and 1,4-disubstituted 1*H*-1,2,3-triazoles with conservation of the amino acid side chains. Schroder and co-workers [126] reported the synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles containing an alternative amide bonds as new class of peptidomimetics. Mironiuk-Puchalska *et al* [127] showed that 1*H*-1,2,3-triazole- derivatives of willardiine exhibit significant binding affinity to hHS1S2I ligand-binding domain of GluR2 receptor ($EC_{50} = 2.90$ μM) and decreased viability of human astrocytoma MOG-G-CCM cells in higher extent than known AMPA antagonist GYKI 52466. Srinivasarao*et al* [128] reported the synthesis and anti-tubercular activity of the series of 3-(((1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)carbonyl)-6-chloro-2-methylquinoxaline-1,4-dioxide analogues. Among them, the compound (**26**) has significant anti-tubercular activity (MIC = 30.35 μM). A series of 1,4-disubstituted-1,2,3-triazoles prepared by de Faria *et al* [129] have inhibitory activities against human glioblastoma (GBM) cell lines,. The results indicate that, the bis-triazole (**27**) found most effective.Sulfonamide is one of the most promising classes of classical carbonic anhydrase inhibitors. Singh and coworkers [130] demonstrated their synthesized series of indolylchalcones

incorporating benzenesulfonamide-1,2,3-triazole (**28**) possesses hCA inhibitory activity against human carbonic anhydrases (hCAs).


(26)   (27)   (28)
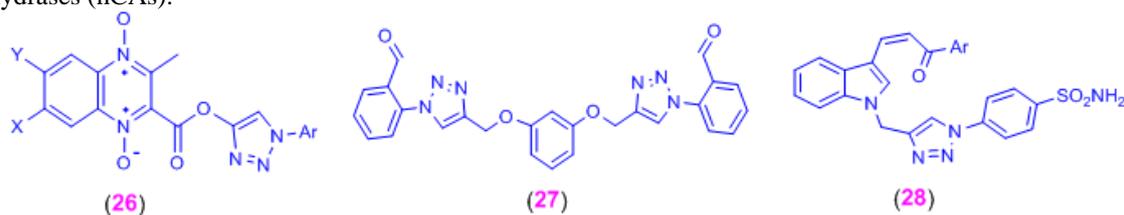
Alzheimer's disease (AD) is a well-known neurodegenerative disorder affecting millions of old people worldwide. In this context, Kaur and co-workers [131] reported that their synthesized series of bis-triazoles are useful as multi-target-directed ligands (MTDLs) against Alzheimer disease (AD). Amongst them, the compound (**29**) having *o*-CF$_3$ group on the phenyl ring displayed most potent inhibitory activity (96.8% inhibition, IC$_{50}$ = 8.065 ± 0.129 μM) against Aβ$_{42}$ aggregation, compared to the reference compound curcumin (95.14%, IC$_{50}$ = 6.385 ± 0.009 μM), it disassembled preformed Aβ$_{42}$ aggregates as effectively as curcumin. Furthermore, it displayed metal chelating ability and significantly inhibited Cu^{2+}-induced Aβ$_{42}$ aggregation and disassembled preformed Cu^{2+}-induced Aβ$_{42}$aggregates, and also controlled the generation of the reactive oxygen species (ROS) by preventing the copper redox cycle.Rastegari*et al* [132] showed that 1,2,3-triazole-chromenone carboxamides have cholinesterase inhibitory activity, in particular *N*-(1-benzylpiperidin-4-yl)-7-((1-(3,4-dimethylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxamide (**30**) has the best acetylcholinesterase inhibitory activity (IC$_{50}$ = 1.80 μM).


(29)   (30)
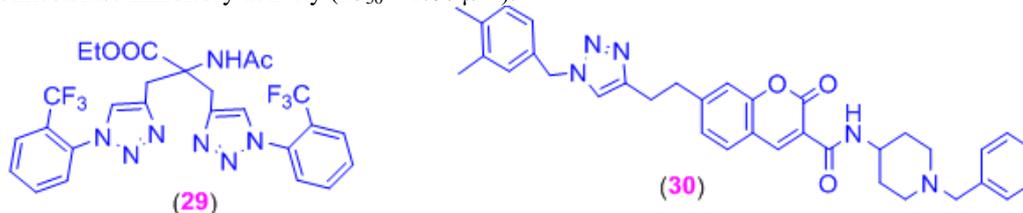
V. Physico-Chemical Properties

Alizadeh co-workers [133] developed an efficient click azide–alkyne [3+2] cycloaddition reaction *via* a three-component one pot reaction of *N*-propargylsulfonamides, sodium azide, and α-haloesters for the synthesis of 1-ester 4-sulfonamide-1,2,3-triazole derivatives (Scheme 34). The mild reaction conditions, avoiding the isolation of hazardous organic azides, good yields (65-78%), and inexpensive starting materials are advantages of the cycloaddition reaction. The report shows that the target compound has Lithium ion affinity of 80.78 kJ/mol higher than its sodium ion affinity. The NICS index confirms the cation π interaction in complex of the synthesized product with Li$^+$ and Na$^+$ ions.

Scheme 34
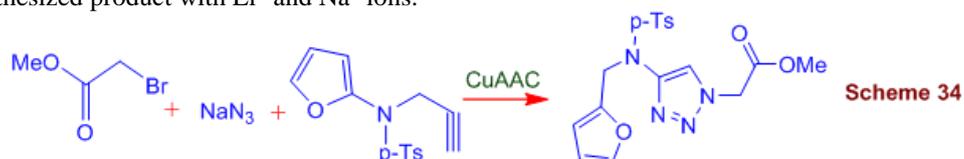
Motornov and co-workers [134] developed a convenient method for arylation of mono- and disubstituted 1,2,3-triazoles by copper-catalyzed Chan-Lam coupling. The method is applicable for the regioselective synthesis of fluorescent 4-halogen-substituted 2,5-diaryl-1,2,3-triazoles. Comparative study of their fluorescent properties revealed that 4-fluorosubstituted triazoles (**31**) possess the highest quantum yield (up to 0.69) among halogenated triazoles possessing Cl and Br in the position 4.Triazole-linked xylofuranose derivatives with pyrene moieties show fluorescence properties towards various cations and anions. Bis-triazoles appended bis-pyrenyl-based sugar derivative (**32**) exhibited selective and sensitive fluorescence quenching effect in the presence of Cu^{2+} ions over a wide range of cations and anions in acetonitrile. The ON-OFF type fluorescence response of (**32**) was explained by the conformational changes from strong excimer emission of pyrene to weak pyrene monomer emission due to an interaction between Cu^{2+}and inward-facing triazole groups (Scheme 35) [135].
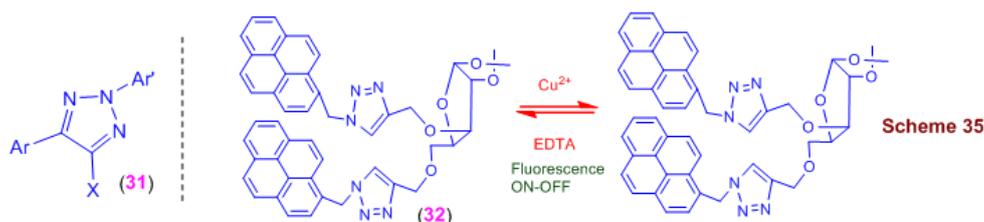
A series of thirty closely related polyfluoroalkyl-substituted glycosidyl-1,2,3-triazoles (**33**) with systematic variations in the type of sugar, D-glucos-1′-yl or D-galactos-6′-yl derivatives, have been studied for physicochemical properties like the length and nature of linker groups to the triazole, the point of attachment and the atom of attachment between the substituent and the triazole, and the length of the perfluoroalkyl chain. The study revealed that these analogues might acts as interconvertible fluorous surfactants [136]. The polyfluoroalkyl-substituted 1-β-D-glucosyl and 6-D-galactosyl 1,2,3-triazoles are candidates for fluorous surfactants that are switchable between amphiphilic partner states, hydrophobic in the case of protected sugars and hydrophilic in unprotected sugars [137]. Baker *et al* [138] designed triazole 1,5-linkage that mimics the phosphodiester backbone in DNA using a ruthenium catalyst, and the artificial linkage was incorporated into a DNA backbone *via* a phosphoramidite building block (**34**). They studied the biophysical properties of DNA with a 1,5 triazole linkage in the backbone by UV melting and circular dichroism. The result shows that the artificial linkage only slightly destabilises duplexes made with complementary DNA or RNA targets.
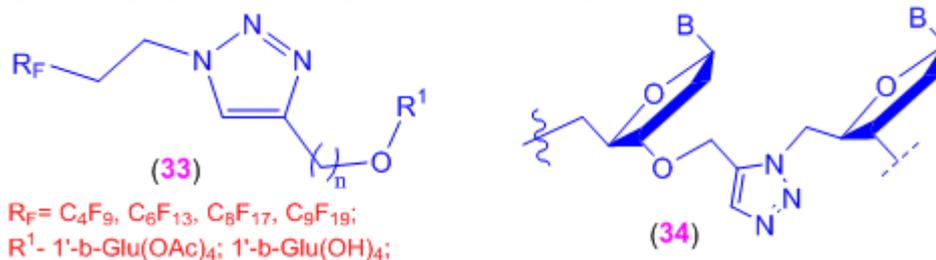
VI. Conclusion

During the past two decades, the CuAAC reaction has become a powerful tool for the synthesis of a large number of 1,2,3-triazoles and has led to applications in almost every field of chemistry and biochemistry. In this review, we summarized the recent progress in the synthetic protocols along with various popular related reactions. The emphasis was given to molecular hybrids and their implications on biological activities, as well as physic-chemical properties of 1,2,3-triazoles. The pharmacological potencies associated with the triazoles, with special attention on antimicrobial, anticancer, anti-inflammatory, anti-proliferative, and antidiabetic activities were also summarized. As a whole, the collection, compilation, and presentation of the summary in this review article will surely help the new researchers working and intended to work in this area of 1,2,3-triazoles.

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