Chapter

1,2,3-Triazoles: Synthesis and Biological Application

Abdul Aziz Ali

Abstract

Among nitrogen-containing heterocyclic compounds, 1,2,3-triazoles are privileged structure motif and received a great deal of attention in academics and industry. Even though absent in nature, 1,2,3-triazoles have found broad applications in drug discovery, organic synthesis, polymer chemistry, supramolecular chemistry, bioconjugation, chemical biology, fluorescent imaging, and materials science. Therefore, the development of facile and straightforward methodology for the synthesis of 1,2,3-triazoles is of noteworthy interest. In this study, emphasis will be given to numerous synthetic approaches for the synthesis of 1,2,3-triazoles, especially the popular click chemistry approach. Furthermore, several biological activities of this promising heterocycle will also be discussed.

Keywords: 1,2,3-triazoles, click chemistry, organocatalysis, biological activity, drug discovery

1. Introduction

Nitrogen-containing heterocyclic compounds are indispensable for life as they are part of essential building blocks like amino acids, nucleotides, etc. 1,2,3-Triazoles are one of the most important nitrogen-containing five-membered heterocycles and have a wide range of applications in pharmaceuticals, supramolecular chemistry, organic synthesis, chemical biology and industry [1–6]. The 1,2,3-triazoles has numerous useful properties like high chemical stability (usually inert to acidic or basic hydrolysis as well as oxidizing and reducing conditions even at high temperature), aromatic character, strong dipole moment (4.8–5.6 Debye), and hydrogen bonding ability [7]. These spectacular features make the substituted 1,2,3-triazole motif structurally resembling to the amide bond, mimicking an E or a Z amide bond. Many prominent medicinal compounds having a 1,2,3-triazole core are available in the market like anticonvulsant drug Rufinamide, broad spectrum cephalosporin antibiotic cefatrizine, an anticancer drug carboxyamidotriazole and β-lactum antibiotic tazobactam, etc. [8].

2. Synthesis of 1,2,3-triazoles

Owing to its versatile applications, the synthesis of 1,2,3-triazoles has been a subject of extensive research. The synthetic methodologies for the preparation of this important scaffold can be broadly divided into four categories (**Figure 1**) [9]:

i. Huisgen 1,3-dipolar cycloaddition

ii. Metal-catalyzed 1,3-dipolar cycloaddition

iii. Strain-promoted azide alkyne cycloaddition

iv. Metal-free synthesis of 1,2,3-triazoles

2.1 Huisgen 1,3-dipolar cycloaddition

Huisgen 1,3-dipolar cycloaddition was the most straightforward and atom-economical synthesis of 1,2,3-triazoles. However, elevated reaction temperature and poor regioselectivity (mixtures of 1,4- and 1,5-isomers) make this process unsatisfactory [10].

2.2 Metal-catalyzed 1,3-dipolar cycloaddition

In 2001, Sharpless et al. coined the term "Click Chemistry," a set of highly reliable, practical, and selective reactions for the rapid synthesis of valuable new compounds and combinatorial libraries. The click reaction should be *modular, with*

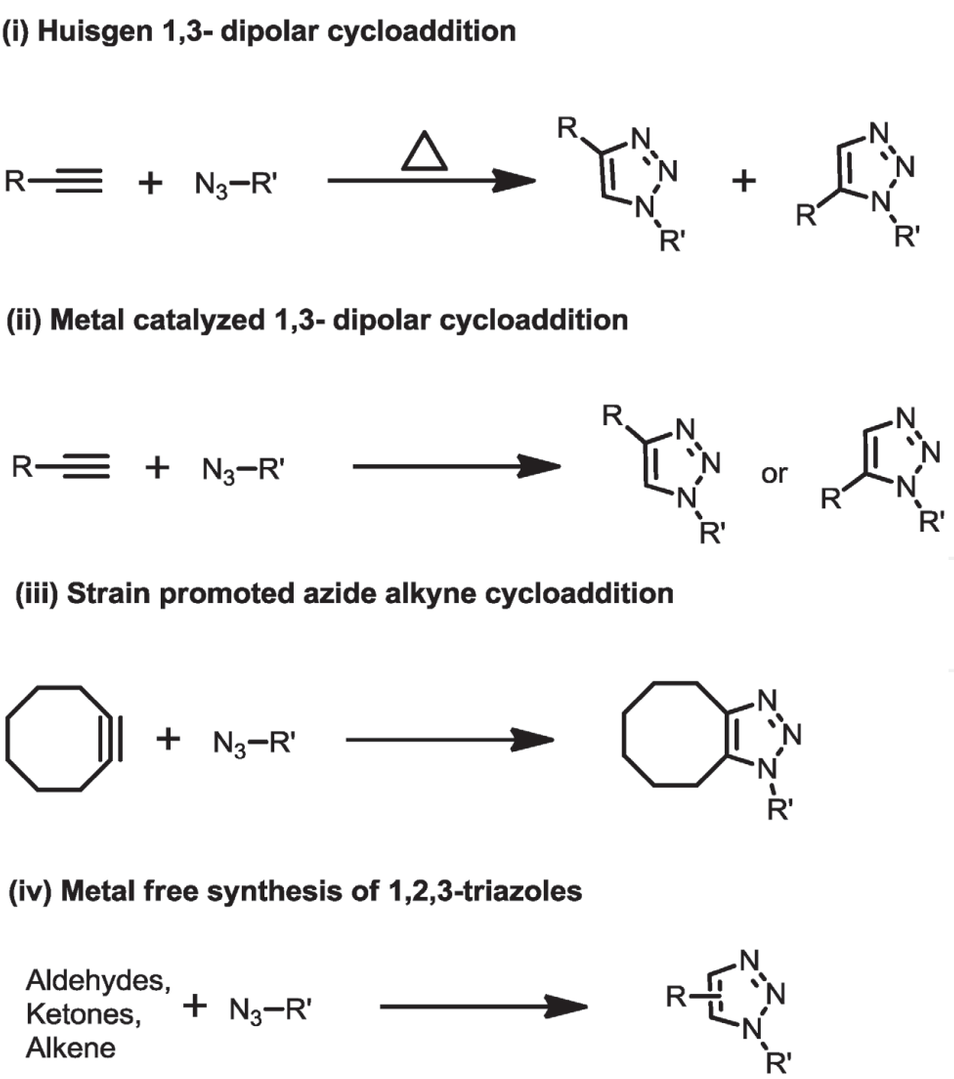
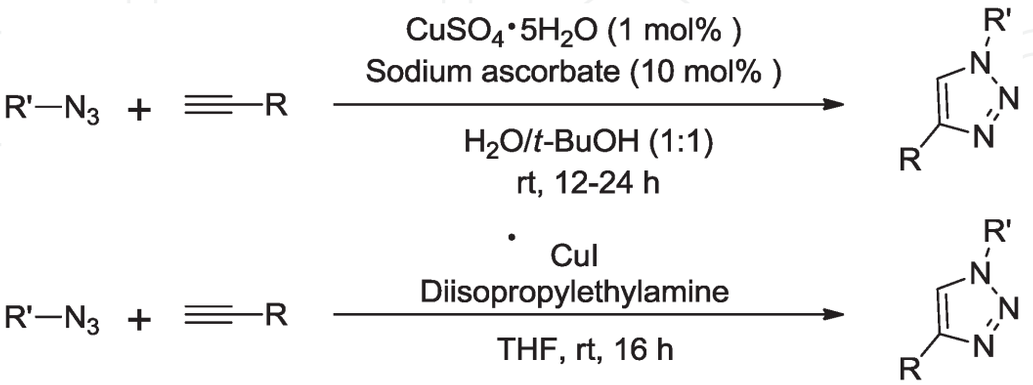
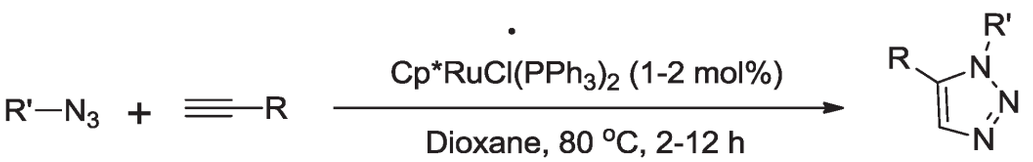


Figure 1.
Strategy of the synthesis of 1,2,3-triazoles.

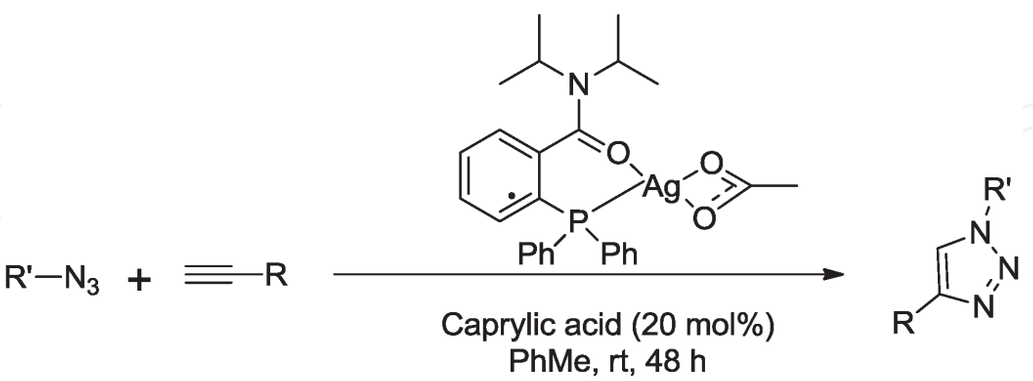
high yield, wide in scope, generate only innocuous by-products (that can be removed without chromatography), stereospecific, easy to carry out and that need benign solvent [11]. In 2002, the groups of Sharpless and Meldal independently revealed a copper-catalyzed variant of Huisgen's azide-alkyne cycloaddition (CuAAC reaction) identified as one of the prime example of click chemistry in the literature [12, 13]. The unique advantages of CuAAC reaction are excellent substrate scope, prominent atom economy, good regioselectivity (only 1,4-isomer), high yield of products and mild reaction conditions [14–17].



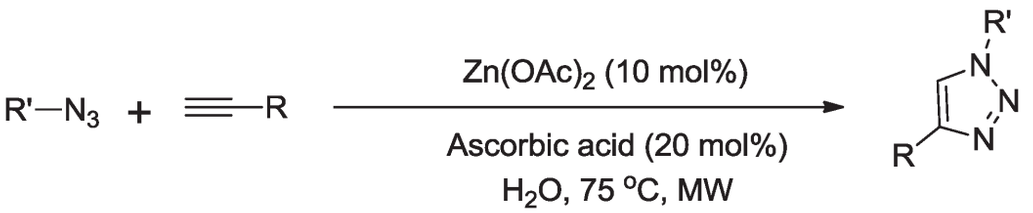
In 2005, Fokin and coworkers devised an efficient approach for the construction of 1,5-disubstituted 1,2,3-triazoles by ruthenium cyclopentadienyl complexes (RuAAC). In addition, internal alkynes also effective in this protocol leading to fully substituted 1,2,3-triazoles [18].



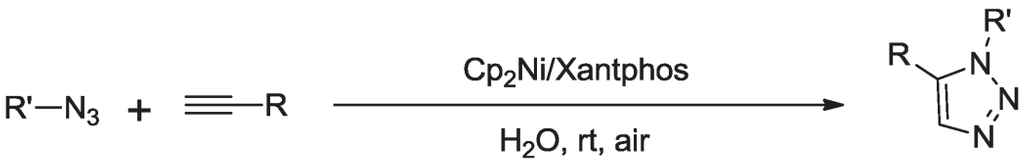
The McNulty group reported a well-defined Ag(I) complex for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles at room temperature [19].



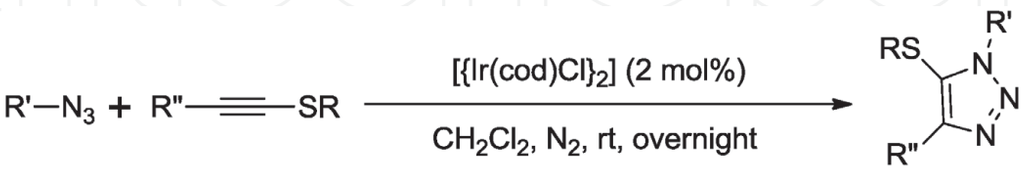
An interesting $Zn(OAc)_2$-catalyzed azide-alkyne cycloaddition was developed by Postnikov and his research group affording 1,4-disubstituted 1,2,3-triazoles [20].



In 2017, Kim et al. devised Cp_2Ni/Xantphos catalytic method to access 1,5-disubstituted 1,2,3-triazoles under mild condition [21].

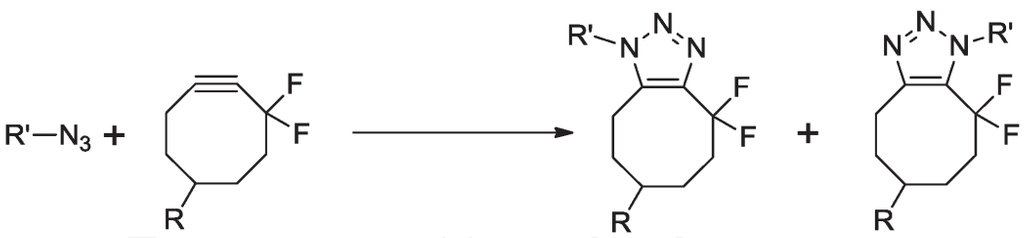


Sun and coworkers reported intermolecular iridium-catalyzed azide-alkyne cycloaddition reaction (IrAAC) of electron-rich internal alkynes [22].



2.3 Strain-promoted azide alkyne cycloaddition

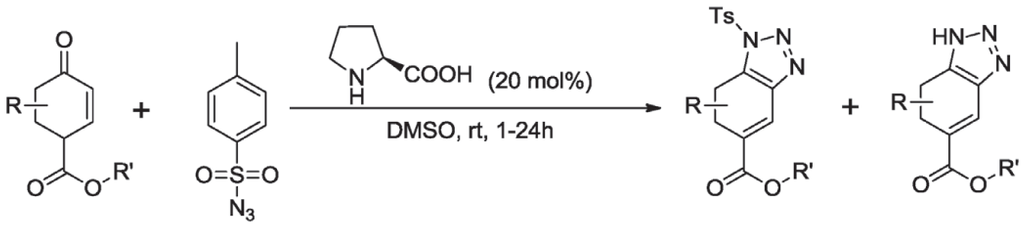
Despite the overwhelming popularity of click chemistry in modern science and technology, the using of metals creates serious concern in biological system due to cellular toxicity. The Bertozzi group explored an interesting protocol of strain-promoted azide-alkyne cycloaddition (SPAAC) reaction for bioconjugation. The driving force for this reaction was the release of large ring strain in the cycloalkynes which proceeds under physiological condition without any catalyst [23].



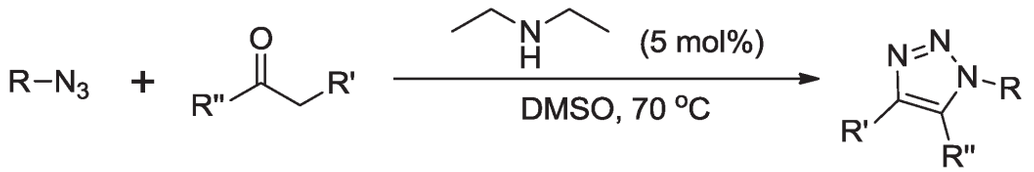
2.4 Metal free synthesis of 1,2,3-triazoles

Organocatalytic reactions has gained considerable attention in the synthesis of 1,2,3-triazoles using enamines, enolates as dipolarophiles. Besides, activated alkenes were established as a useful substrate for triazole formation.

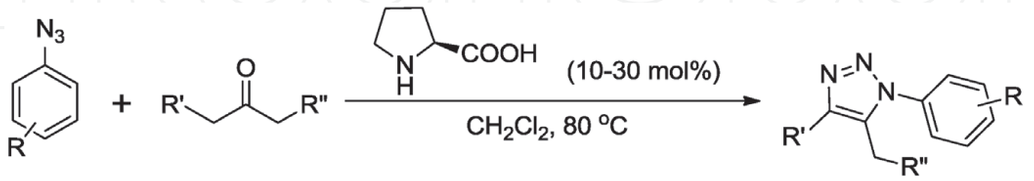
Ramachary and coworkers developed L-proline-catalyzed synthesis of 1,2,3-triazoles via an enamine mediated [3 + 2]-cycloaddition reaction [24].



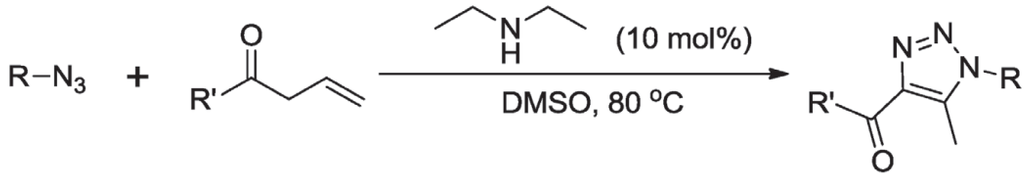
In 2011, the regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles was achieved by Wang et al. using an organocatalytic enamine azide reaction [25].



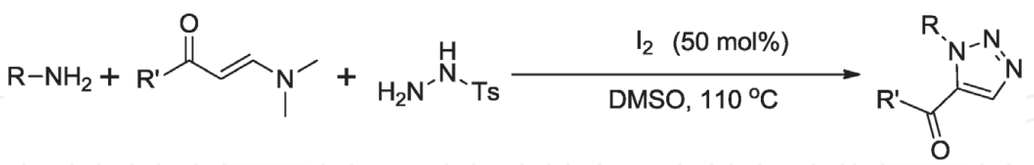
The Bressy group reported synthesis of substituted 1,2,3-triazoles from unactivated ketone and aromatic azide using microwave condition [26].



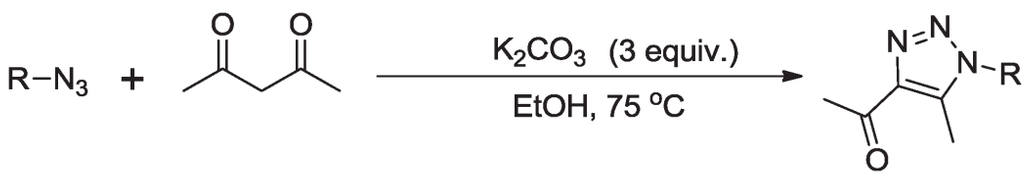
Wang and coworkers devised an organocatalytic method for the preparation of fully substituted 1,2,3-triazoles by diethylamine-catalyzed reaction of azides and allyl ketones [27].



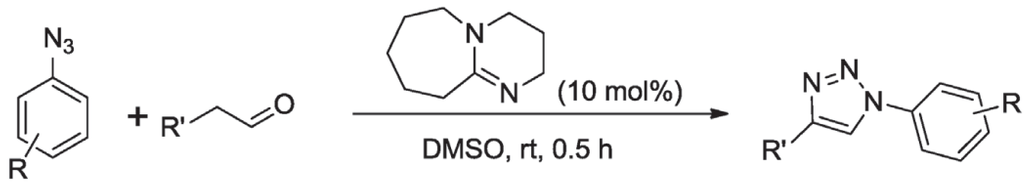
Iodine mediated, oxidant free synthesis of 1,5-disubstituted 1,2,3-triazoles was reported by the Wan group using primary amines, enamines and tosylhydrazine [28].



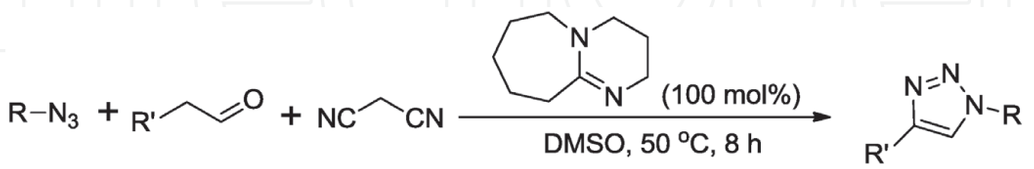
Using potassium carbonate, Kannan and co-workers developed a protocol for the synthesis of 4-acetyl-5-methyl-1,2,3-triazoles from acetylacetone and aromatic azides [29].



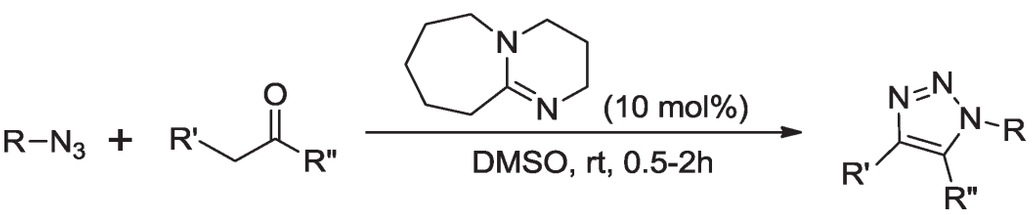
The Ramachary group described an efficient methodology for the preparation of 1,4-disubstituted 1,2,3-triazoles using organocatalytic azide-aldehyde [3 + 2] cycloaddition reaction [30].



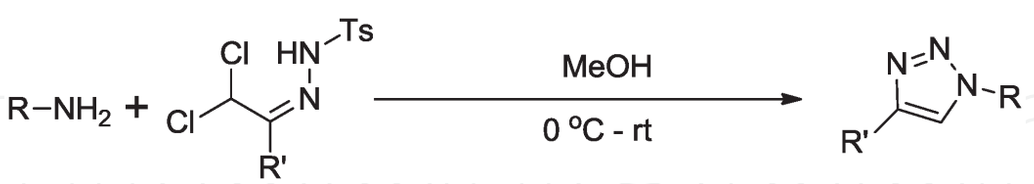
Paixão et al. reported the use of alkylidenemalononitriles in 1,3-dipolar cycloaddition with aromatic azides mediated by DBU [31].



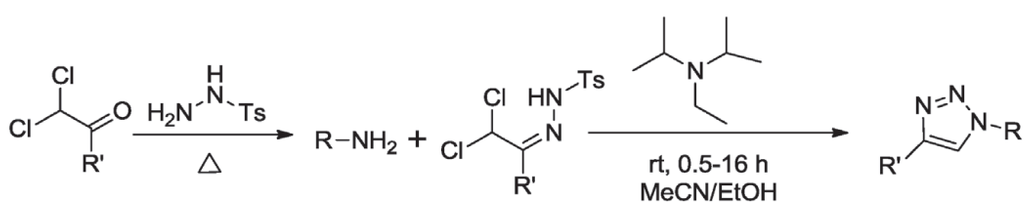
In their another pioneering work, Ramachary and coworkers reported an interesting organocatalytic [3 + 2]-cycloaddition reaction of ketones with azides for synthesis of fully substituted 1,2,3-triazoles [32].



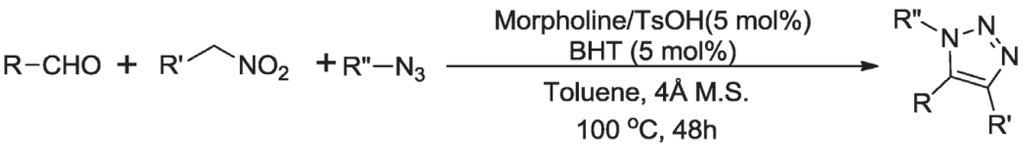
In a methodology published in 1986, Sakai et al. used primary amines and α,α-dichloro ketone derived tosylhydrazones for the metal free synthesis of 1,2,3-triazoles [33].



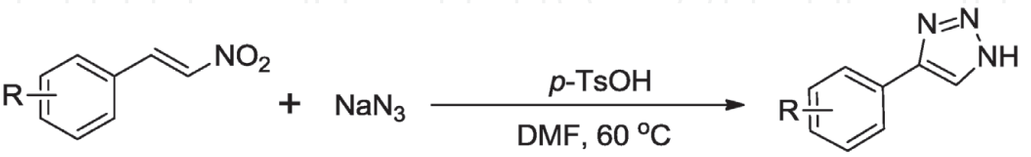
Westermann and co-workers developed a cascade reaction using α,α-dichloro-tosylhydrazones and primary amines in the presence of diisopropylethylamine [34].



Metal free regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles was reported by Dehaen et al. from aldehydes, nitroalkanes and organic azides [35].



The Guan group developed p-toluenesulfonic acid-catalyzed 1,3-dipolar cycloaddition reaction for the synthesis of 4-aryl-NH-1,2,3-triazoles from nitroolefins with sodium azide [36].



3. Biological activity of 1,2,3-triazoles

1,2,3-triazoles are stable towards metabolic degradation and easily form hydrogen bonding which can increase solubility favoring the binding of biomolecular targets. Owing to their unique properties, 1,2,3-triazoles are attractive building blocks in drug discovery.

3.1 Anti-cancer activity

Cancer is a major public health concern and second leading cause of mortality globally. Despite that numerous anticancer agents including taxol, vincristine, vinblastine, camptothecin derivatives, topotecan are available, search for novel compounds with different modes of actions has received significant interest.

Kallander et al. reported 4-aryl-1,2,3-triazoles **1** as inhibitors of human methionine aminopeptidase type 2 (hMetAP2). The anticancer activity of these molecules is due to the N1 and N2 nitrogen atoms of the triazole moiety that actively contribute in binding to the active site of enzyme [37].

Odlo and coworkers disclosed a series of cis-restricted 1,5-disubstituted 1,2,3-triazole analogues of combretastatin A-4. One of the triazole derivatives **2** showed effective cytotoxic activity against various cancer cell lines with IC_{50} values in the nanomolar range. Molecular docking study shows that the triazole moiety interacts with β-tubulin via H-bonding with numerous amino acids [38].

The series of triazole-modified 20,30-dideoxy-20,30-diethanethioribonucleosides **3** displayed considerably better antitumor activity towards HepG2, A549, and Hela cell lines and higher cytotoxicity towards HepG2, LAC, and Hela cell lines compared to the control drug floxuridine [39].

Rangappa and coworkers prepared a series of 1,2-benzisoxazole tethered 1,2,3-triazoles **4** and established its noteworthy antiproliferative effect against human acute myeloid leukemia (AML) cells. Using MTT assay, 3-(4-(4-phenoxyphenyl)-1H-1,2,3-triazol-1-yl)benzo[d]isoxazole was found to be the most potent antiproliferative agent with an IC_{50} of 2 μM against MV4-11 cells [40].

Using "click chemistry" approach, the Miller group prepared a series of N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)arylamides and examined their antiproliferative activity. One of the compound **5** displayed an IC_{50} of 46 nM against MCF-7 human breast tumor cells [41].

Lin and coworkers synthesized a series of heterocycle-fused 1,2,3-triazoles and evaluated their cytotoxic activity. With IC_{50} values lower than 1.9 μg/mL against A431 and K562 human tumor cell lines, 4-Methoxyphenyl substituted 1,3-oxazoheterocycle fused 1,2,3-triazole **6** was found to be the most potent derivative [42].

1,2,3-triazole derivatives of betulinic acid were synthesized by Koul et al. and their cytotoxic activity against nine human cancer cell lines was evaluated (**Figure 2**). Two molecules **7** and **8** exhibited notable IC_{50} values (2.5 and 3.5 μM, respectively) against leukemia cell line HL-60 (5–7-fold higher potency than betulinic acid) [43].

3.2 Anti-inflammatory activity

Inflammation is particularly complex biological process of body tissues, where membrane-bound phospholipids release arachidonic acid (AA), followed by

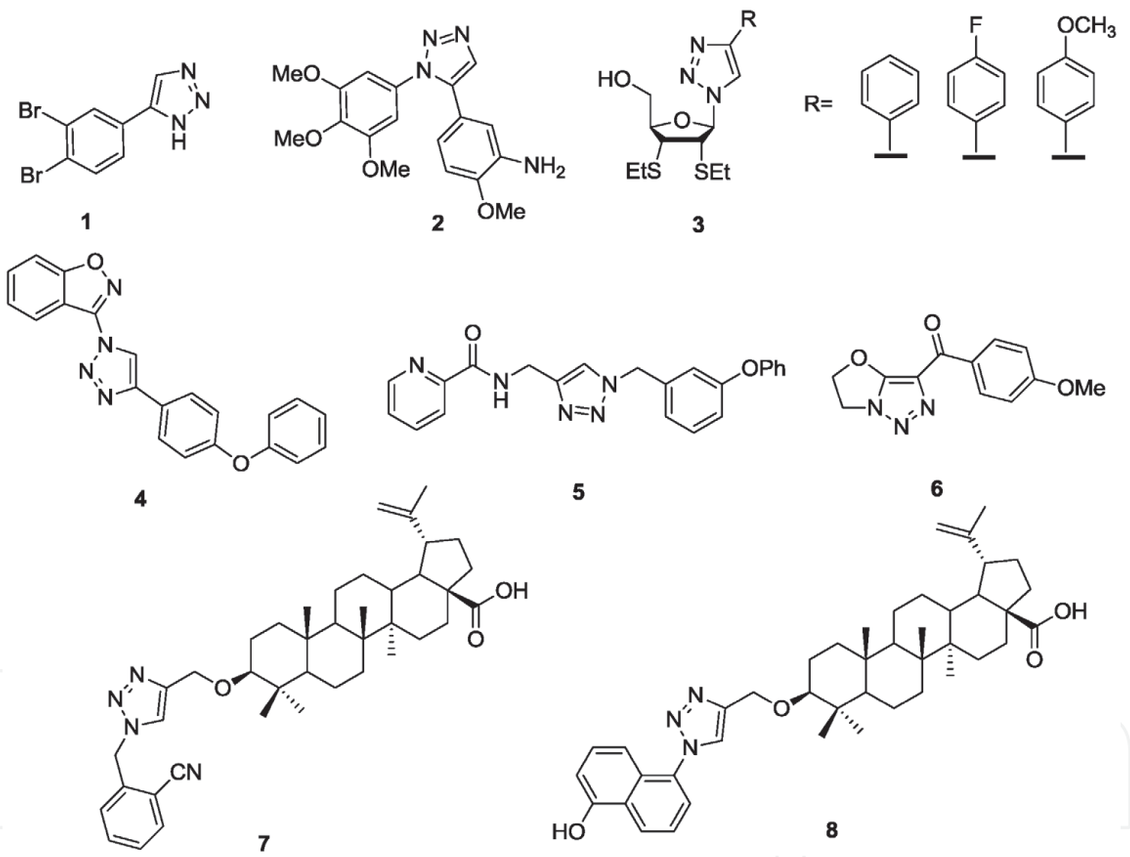


Figure 2.
Some examples of 1,2,3-triazole containing molecules with anticancer activity.

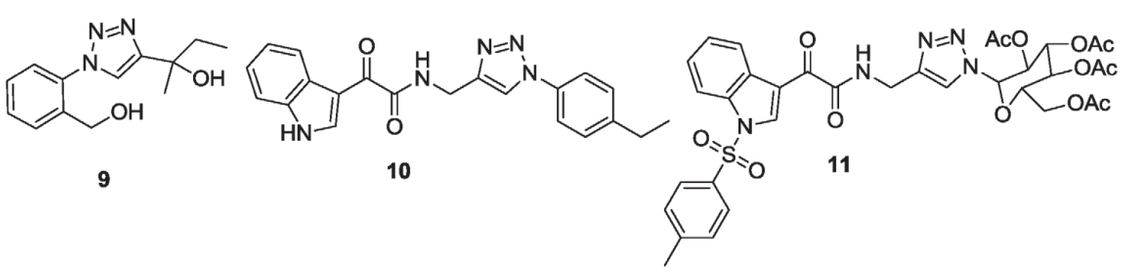


Figure 3.
Various examples of 1,2,3-triazole containing molecules with anti-inflammatory activity.

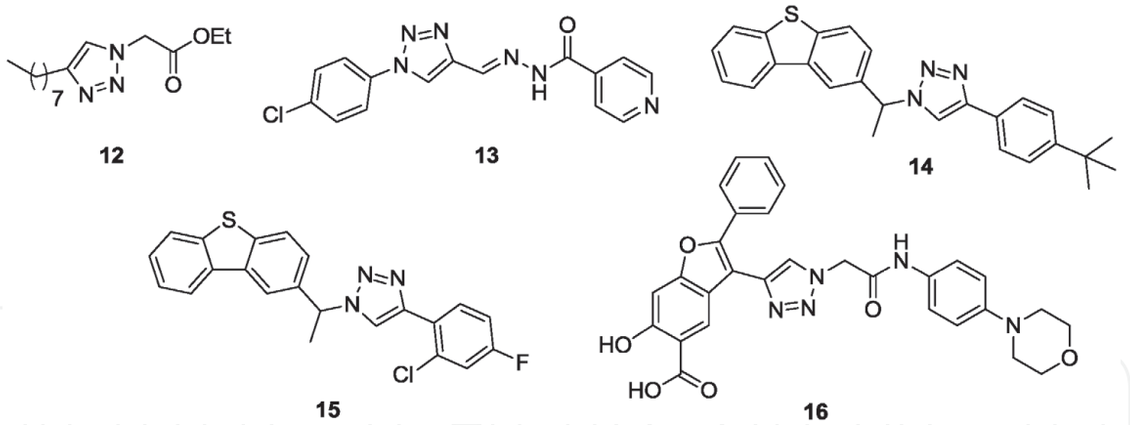


Figure 4.
Representative examples of 1,2,3-triazole containing molecules with antitubercular activity.

biotransformation processes using cycloxygenase (COX) and 5-lipoxygenase (5-LOX) pathways. Several non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, ibuprofen, and naproxen block arachidonic acid metabolism by obstructing cycloxygenase. Nevertheless the side effects associated with these drugs prompted medicinal chemists to develop alternative scaffolds.

The Jung group synthesized twenty-four phenyl-1H-1,2,3-triazole derivatives and studied their biological activity. At the same dose of 25 mg/kg, compound **9** showed more compelling effects than the existing anti-inflammatory drug diclofenac [44].

Yar and coworkers reported 1,2,3-triazole tethered Indole-3-glyoxamide derivatives for in vivo anti-inflammatory activity using click chemistry approach. Two compounds **10** and **11** displayed excellent inhibition of COX-2 (IC_{50} 0.12 μM) with good COX-2 selectivity index (COX-2/COX-1) of 0.058 and 0.046, respectively (**Figure 3**) [45].

3.3 Antitubercular activity

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is one of the infectious contagious disease and remains a serious risk to public health worldwide. Generally, the direct observed therapy strategy (DOTS) is the treatment for TB, but the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) developed challenges. Therefore identifying of effective anti-TB drug candidates has received enormous interest.

Labadie and coworkers used click chemistry to synthesize a small library of 1,2,3-triazole derivatives and screened them against *Mycobacterium tuberculosis* and *Mycobacterium avium*. The biological screening indicated that the triazole **12** displayed more significant activity against *M. tuberculosis* than standard drug [46].

Using click chemistry, the Boechat group reported 4-substituted N-phenyl-1,2,3-triazole derivatives for antimicrobial activity against *Mycobacterium tuberculosis* strain H37Rv (ATCC 27294). Derivatives of isoniazid, (E)-N′-[(1-aryl)-1H-1,2,3-triazole-4-yl)methylene] isonicotinoyl hydrazides, **13** revealed significant activity with minimum inhibitory concentration (MIC) value of 0.62 μg/mL [47].

The Kantevari group described a molecular hybridization approach for the synthesis of triazole clubbed dibenzo[b,d]thiophene-based *Mycobacterium tuberculosis* inhibitors. The most potent compounds **14** and **15** in check of their *in vitro* activity against *M. tuberculosis* strain H37Rv exhibited MIC = 0.78 μg/mL [48].

Zhang et al. synthesized triazole-based library of benzofuran salicylic acid derivatives using click chemistry strategy. The compound **16** was found to be potent antiTB therapeutic with efficient cellular activity (**Figure 4**) [49].

3.4 Antimicrobial activity

Fungal and bacterial infections create severe apprehension for human and animal survival. The inefficacy of available drugs and rising resistant strains demand significant interest into new classes of antimicrobial agents.

Agarwal and coworkers synthesized 1,2,3-triazole derivatives of chalcones and flavones by click chemistry and screened their antimicrobial and antiplasmodial activity. Several compound including **17** showed promising antifungal and antibacterial activity [50].

The Murugulla group studied antimicrobial activity of theophylline containing 1,2,3-triazoles with variant nucleoside derivatives. Compound **18** was shown to be potent and effective against three bacterial strains *B. cereus*, *Escherichia coli* and *P. aureoginosa* with MIC values of 0.0156, 0.03125, 0.0625 mg/mL and compound **19** with MIC values of 0.03125, 0.0156, 0.0625 mg/mL was found to be effective against *S. aureus, B. cereus* and *Escherichia coli*, respectively [51].

Diaryl sulfone containing novel 1,2,3-triazoles were synthesized by Jørgensen and coworkers and their biological evaluation was carried out as well. Compound **20** was found to be the most potent antifungal agents with MIC at 25 μg/mL [52].

Zhou et al. reported a series of 1,2,3-triazole-derived naphthalimides for potential antimicrobial activity. Bioactive assay revealed that **21** showed better anti-*Escherichia coli* activity than existing drugs Norfloxacin and Chloromycin [53].

5-nitrofuran—triazole congener—was prepared by the Kamal group and its biological activity was studied. Among the other compounds, **22** exhibited promising antibacterial activity (MIC value of 1.9 μg/mL against different bacterial strains)

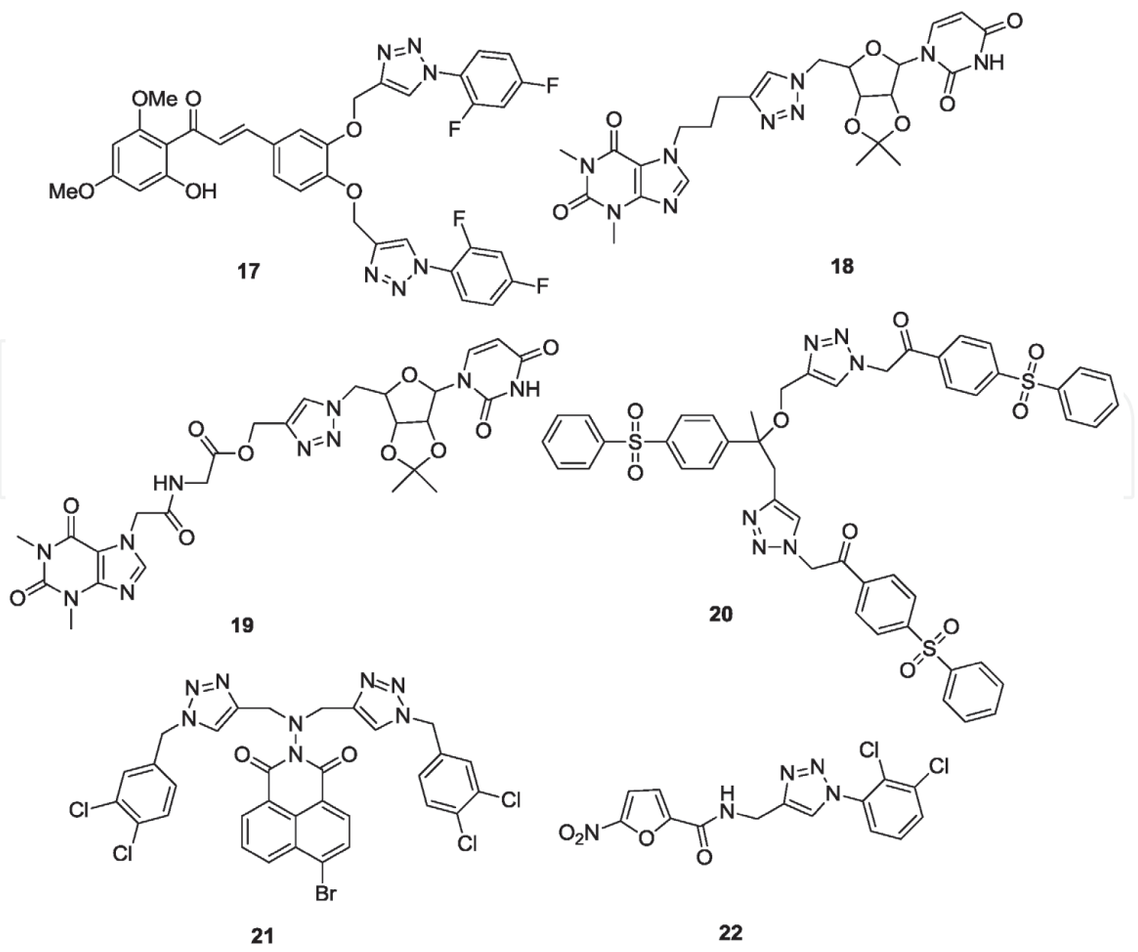


Figure 5.
Representative examples of 1,2,3-triazole containing molecules with antimicrobial activity.

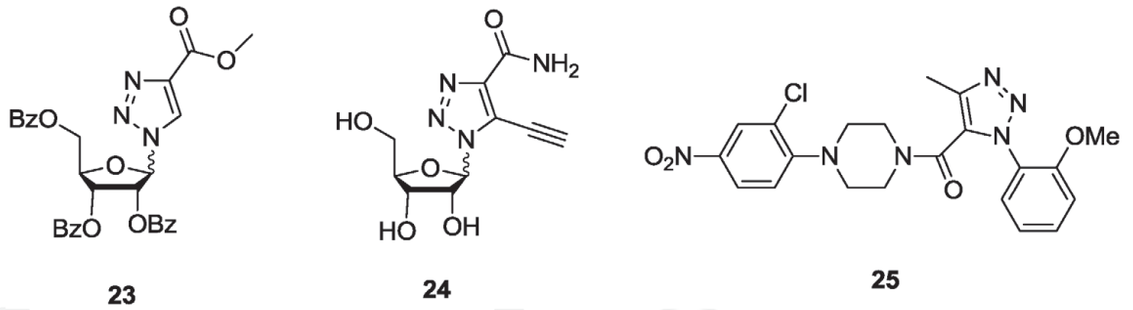


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Figure 6.
Examples of 1,2,3-triazole containing molecules with antiviral activity.

and antifungal activity (MIC = 3.9 μg/mL) compared to the standard miconazole (MIC = 7.8 μg/mL) against *C. albicans* and *C. parapsilosis* (**Figure 5**) [54].

3.5 Antiviral activity

Viral diseases are caused by viruses infecting an organism body. Although vaccines and antiviral drugs are used for treating viral infections, advance of novel viruses creates health risk over the world. Therefore development of alternative antiviral agents is of significant interest.

Boechat and coworkers reported the synthesis of 1,2,3-triazole nucleoside ribavirin analogs and studied their antiviral activity. The synthesized compound **23** displayed potent activity with IC_{50} values 14 and 3.8 μM for Influenza A and reverse transcriptase (RT) from human immunodeficiency virus type 1 (HIV-1 RT), respectively [55].

Ribavirin analogues—4,5-disubstituted 1,2,3-triazole nucleosides—were synthesized by Zeidler et al. and screened for their biological activity. 5-ethynyl nucleoside **24** exhibited effective virus-inhibitory activity against influenza A (H1N1, H3N2 and H5N1), influenza B, measles and respiratory syncytial viruses [56].

The Ding group targeted virus nucleoprotein and synthesized 1,2,3-triazole-4-carboxamide derivatives for anti-influenza drug development. The compound **25**, inhibited the replication of various H3N2 and H1N1 influenza A virus strains with IC_{50} values ranging from 0.5 to 4.6 μM (**Figure 6**) [57].

4. Conclusion

In summary, 1,2,3-triazole moiety has proven to be a privileged scaffolds in medicinal chemistry. The exceptional properties of this promising heterocycle facilitate its wide range of applications from material science to bioconjugation. Thanks to Sharpless for introducing "Click Chemistry," one of the most prevailing tools in drug discovery, chemical biology, and proteomic applications and undoubtedly opens new avenue to the scientific community towards the improvement of life.

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Conflict of interest

There are no conflicts to declare.

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