An overview of synthetic approaches and the potential bioactivity of different 1,2,3-triazole hybrids

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1,2,3-Triazole is considered to be the lead structure for the discovery of many drug molecules. 1,2,3-Triazole has received considerable attention in the field of drug discovery due to its remarkable widespread biological potential. This work summarizes the current synthetic pathways adopted for the synthesis of diverse analogs of 1,2,3-triazole. It also introduces an overview of the latest advances in 1,2,3-triazole hybrid models with various pharmacological activities, their chemical structures, structure–activity relationships, and mechanisms of action.

Keywords:
1,2,3-Triazole, metal-catalyzed synthesis, metal-free synthesis, biological activities

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Introduction

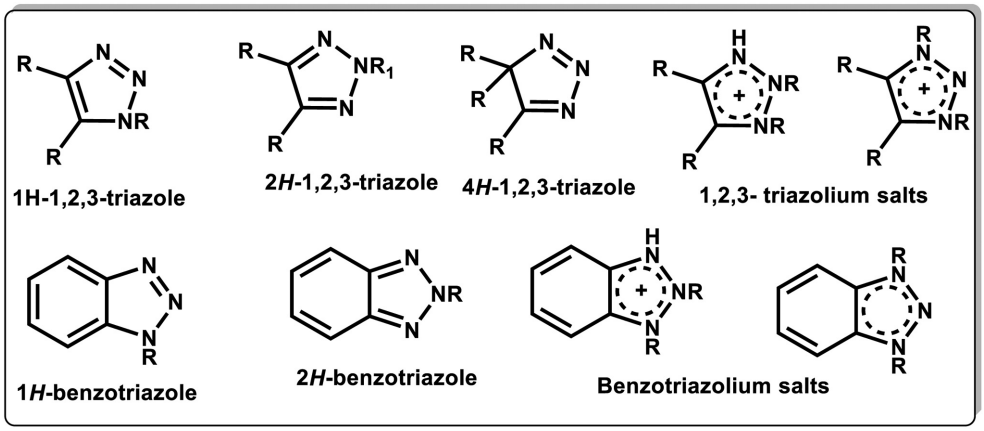
One of the most crucial domains in medicinal chemistry is the investigation of bioactive molecules that contain nitrogen atoms and belong to the category of heterocyclic compounds. In a large variety of pharmacological scaffolds, **1,2,3-triazole** (Fig. 1) has been recognized as a potential heterocyclic component. It has a five-membered nitrogen heterocycle core with two carbon atoms and three nitrogen atoms, and this core significantly affects the biological activity. The existence of a nitrogen heteroatom in the lead compound influences its reactivity as a potential drug, and this, in turn, affects the interactions between the lead compound and various target inhibitors, ultimately influencing pharmacokinetics and metabolism [1]. 1,2,3-Triazoles' significance is derived from their aromatic nature; they resist metabolic degradation, are stable to acid/basic hydrolysis, and are resistant to reduction and oxidation [2]. Triazoles can be found in two isomeric forms: 1,2,3-triazole and 1,2,4-triazole. As shown in Fig. 1, 1,2,3-triazoles are typically further split into three primary classes: monocyclic 1,2,3-triazoles, benzotriazoles, and 1,2,3-triazolium salts [3–6]. Monocyclic 1,2,3-triazoles and benzotriazoles are extremely resistant to hydrolysis, oxidative/reductive conditions, and enzymatic degradation; but, under forcing conditions, reductive cleavage occurs, resulting in the creation of triazolium salts [7,8].

Novel classes of 1,2,3-triazole-containing hybrids and conjugates were developed and investigated as lead drugs for a variety of biological targets. These active ingredients have been confirmed to be anticancerous, antimicrobial, antitubercular, antiviral, antidiabetic, antimalarial, and antileishmanial, and neuroprotective agents are numerous examples of commercially available drugs that contain 1,2,3-triazole moiety (Fig. 2**)** [9].

Due to their unique properties of hydrogen bond formation, dipole–dipole, and stacking interactions with various biological targets, triazole compounds have gained significant importance in the field of medicinal chemistry [10,11].

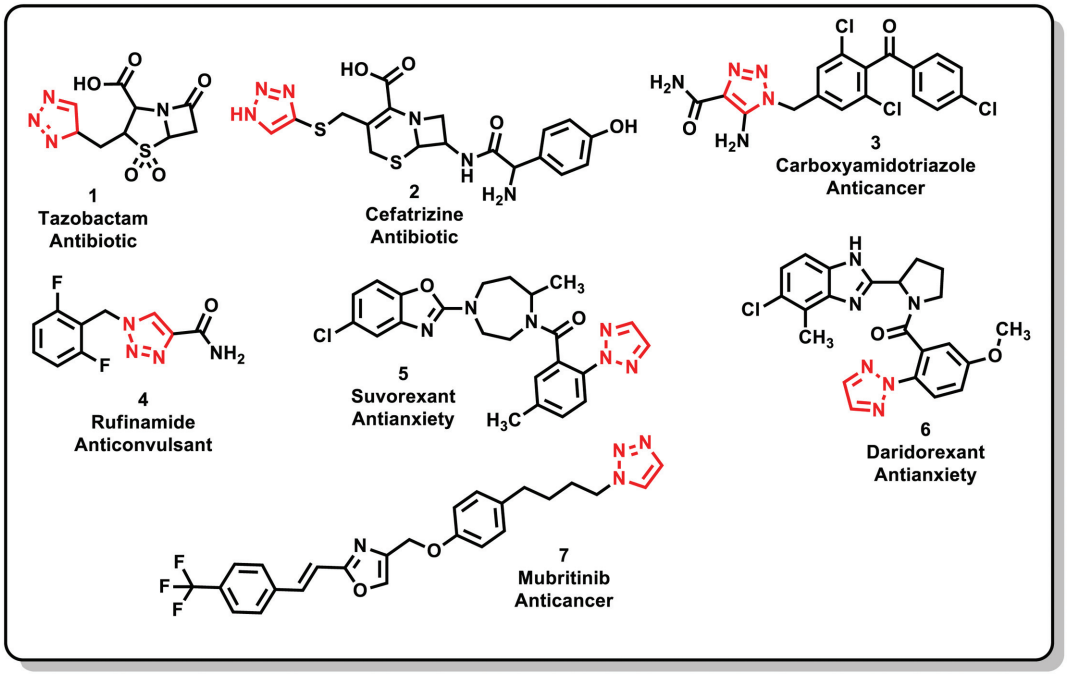
In addition, the 1,2,3-triazole moiety also functions as a crucial synthetic intermediate in a variety of industrial applications, including agrochemicals [2,12], corrosion inhibitors [13,14], additives [15,16], dendrimer polymers[17–20], liquid crystals [21,22], photostabilizers [23,24], pigments [25,26], supramolecular chemistry [27], as well as metal chelators [28–30]. The medicinal chemistry of this

Figure 1



Classification of 1,2,3-triazole rings.

Figure 2



Examples of FDA-approved drugs containing the 1,2,3-triazole ring.

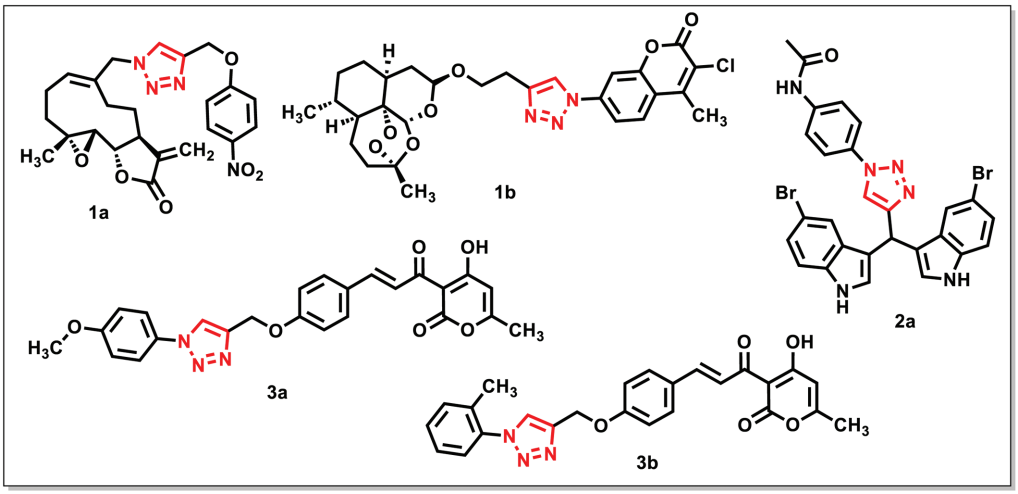
privileged framework should therefore, be updated in the light of the current situation.

Naturally active compounds contain 1,2,3-triazole ring

While the 1,2,3-triazole moiety is not naturally occurring, it has garnered attention as a potential anticancer drug candidate, especially for creating hybrids with 1,2,3-triazole-natural compound combinations. Ding *et al.* successfully synthesized melampomagnolide B-triazole conjugates and assessed their anticancer potential using the Cu_2O nanoparticle-catalyzed 'click' reaction. Compound **1a** (Fig. 3) demonstrated remarkable potency with an IC_{50} value of 0.43 μM, which is approximately 11.5 times more potent than melampomagnolide B (IC_{50}=4.93 μM). Importantly, compound **1a** did not affect normal cells and exhibited significant effects on cancer cells, inducing apoptosis, inhibiting proliferation, and reducing migration [31].

In their study, Yu *et al.* successfully synthesized a series of 1,2,3-triazole-dihydroartemisinin-coumarin hybrids. They then conducted screenings to assess the anticancer potential of these hybrids in two

Figure 3



Examples of naturally active compounds containing the 1,2,3-triazole moiety.

different types of cancer cells. HT-29 and MDA-MB-231 cell lines were somewhat sensitive to these hybrids' cytotoxicity, especially when the atmosphere was hypoxic. Notably, compound **1b** (Fig. 3) exhibited higher activity against HT-29 cells compared with MDA-MB-231 cells (with normoxic IC_{50}=1.5 μM and under hypoxia IC_{50}=0.01 μM). This compound also prevented cancer cells from migrating, stopped HT-29 cells in advance in the G0/G1 phase, significantly reduced their ability to form mitochondrial membranes, and caused them to induce apoptosis [32].

In another study, compounds containing triazole–indole hybrids underwent testing against M. tuberculosis H37Ra, both in active and latent stages, to evaluate their effectiveness in fighting tuberculosis. The results showed that compound **2a** (Fig. 3) displayed the highest activity, with IC_{50} and MIC values of 1 and 3 g/mL, respectively. Specifically, compound **2a** demonstrated superior antitubercular properties against dormant M. tuberculosis H37Ra. Further analysis of structure–activity relationships (SARs) showed that not only compound **2a** but also other indole–triazole conjugates containing bromine exhibited significantly higher potency compared with bis-indole triazoles that lacked bromine [9].

Chalcones have gained recognition as a significant group of compounds, both natural and synthetic, within the flavonoid family. These compounds showcase a wide range of biological activities. The 1,2,3-triazole-chalcone compounds **3a** and **3b** (Fig. 3) exhibited remarkably strong antibacterial and antifungal effects. Their minimum inhibitory concentration (MIC) values ranged from 3.0 to 37 nM. The structure–activity relationship (SAR) analysis revealed that the presence of electron-withdrawing or electron-donating groups on the benzene ring, regardless of their position, significantly improved their effectiveness against a variety of bacterial strains (such as E. coli, P. aeruginosa, S. epidermidis, and B. subtilis) and fungal strains (including C. albicans and A. niger). Hybrids with bromo and methoxy groups also displayed improved activity against the majority of microbes [33].

Researchers have developed numerous novel series of compounds bearing the 1,2,3-triazole moiety using a variety of synthetic methodologies and evaluated their potential biological activity because of the 1,2,3-triazole's fascinating and diversified biological characteristics.

Synthetic Strategies of 1,2,3-triazoles

Huisgen cycloaddition

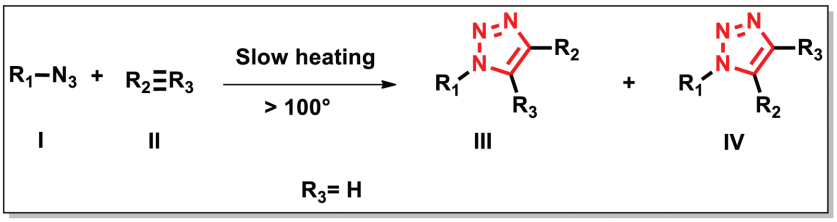
The widely used method to create the 1,2,3-triazole moiety is known as the 1,3-dipolar cycloaddition or Huisgen cycloaddition. This reaction is carried out between an azide **I** and a terminal alkyne **II**, under thermal conditions [34,35]. Due to the poor regioselectivity (1,4- and 1,5-disubstituted 1,2,3-triazoles) **III** and **IV**, minimal chemical performance, and high temperatures [36], it was not applied much in organic synthesis (Scheme I).

Metal-catalyzed synthesis of 1,2,3-triazoles

Copper (I)-catalyzed azide–alkyne cycloaddition (CuAAC)

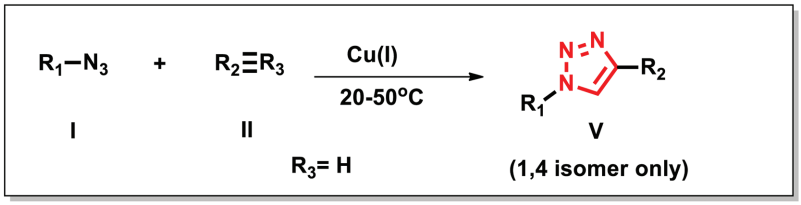
In contrast to the mixture of regioisomers often formed under classical thermal circumstances, only

Scheme I



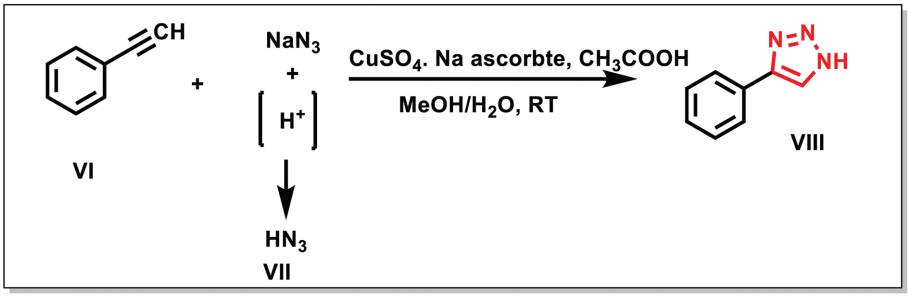
Huisgen cycloaddition: an azide **I** and a terminal alkyne derivative **II**.

Scheme II



Copper (I)- catalyzed azide–alkyne cycloaddition (click chemistry).

Scheme III

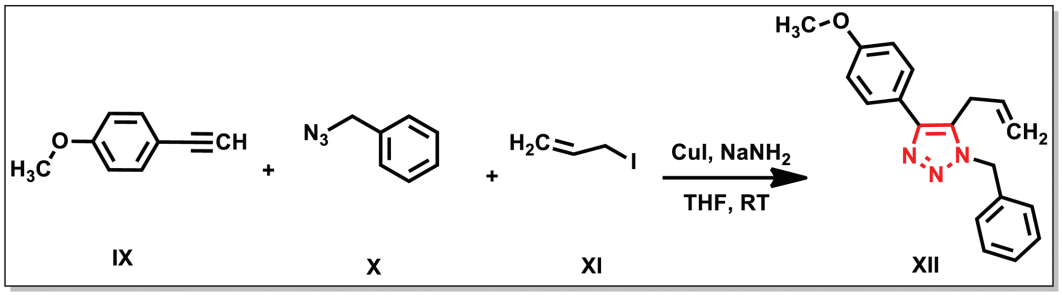


Copper(I)-catalyzed azide–alkyne cycloaddition of HN_3.

the 1,4-disubstituted 1,2,3-triazole regioisomer **V** was produced by Sharpless' click chemistry method's modified copper (I)-catalyzed azide–alkyne cycloaddition reaction (CuAAC) (Scheme II) [34,35].

A recent study has shown the copper-catalyzed azide–alkyne cycloaddition of hydrogen azide (HN_3) **VII** with terminal alkynes **VI** to form 4-substituted-1*H*-1,2,3-triazoles **VIII** (Scheme III), often known as

Scheme IV



Cu(I)-mediated tandem three-component reaction.

NH-1,2,3-triazoles or NH-triazoles, that have shown significant biological uses [37].

Furthermore, another study established a new Cu(I)-mediated tandem three-component reaction (one-pot multicomponent reaction (MCR)) utilizing alkynes **IX**, azides **X**, allyl iodide **XI**, CuI, and $NaNH_2$ at normal temperature, generating a considerable yield of 5-allyl-1,2,3-triazoles **XII** (Scheme IV) [38].

Ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC)

Contrary to thermal 1,3-dipolar cycloaddition, which has a high activation barrier, sluggish, and shows limited regioselectivity, ruthenium (II)-catalyzed reaction of alkynes with azides (RuAAC) has made it simple to generate substituted triazoles [39].

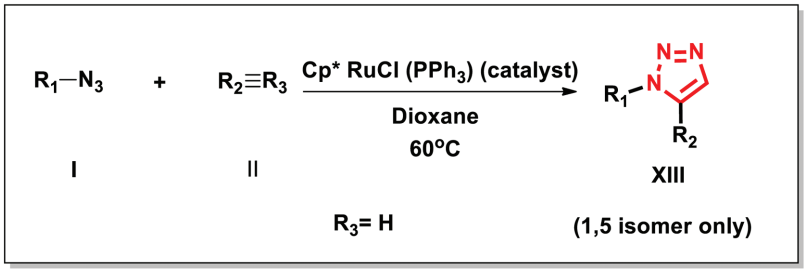
If the reaction occurs when Ru and the cyclopentadiene (Cp) ligand are combined, 1,4 and 1,5-disubstituted triazoles can be produced. When the Cp component was replaced with Cp* (the pentamethyl analog of Cp), 1,5-disubstituted-1,2,3-triazole regioisomer **XIII** was mainly produced 100% of the time (Scheme V) [40].

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

Metal-free [3+2] azide–alkyne cycloaddition/C-N coupling reaction

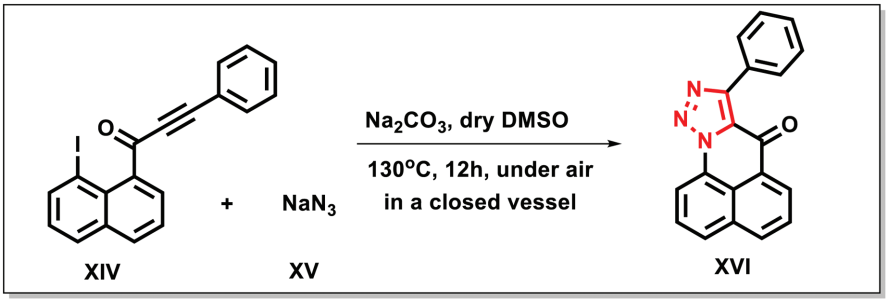
Metals are well-known to cause oxidative damage, metabolic instability, and cellular toxicity in biological systems[41–43]. To date, a variety of metal-free (3+2)-cycloaddition techniques have been created to synthesize 1,2,3-triazoles with various functionalities.

Scheme V



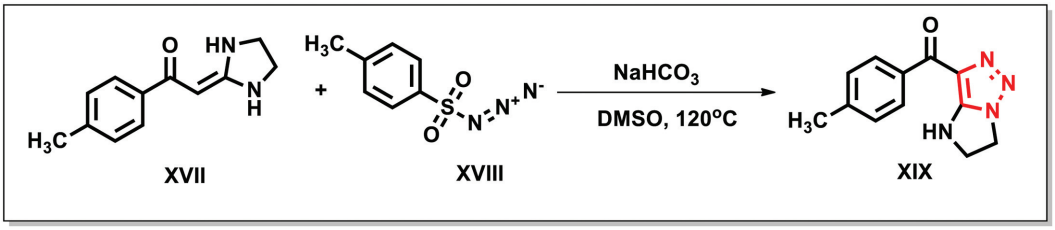
Ruthenium(II)-Catalyzed Azide–Alkyne Cycloaddition.

Scheme VI



Metal-free AAC/C-N bond formation.

Scheme VII



Metal-free synthesis of 1,2,3-triazol-p-tolylmethanone derivative **XIX**.

Majeed *et al*. exhibited that the reaction of (1-(8-iodonaphthalene-1-yl)-3-phenylprop-2-yn-1-one) **XIV** with sodium azide **XV** in dry dimethyl sulfoxide **(DMSO)** at high temperature gave the desired quinolinone ring fused with the 1,2,3-triazole product **XVI** (Fig. 7). But to enhance the yield of the product, the start derivative **XIV** was treated with 1.2 eq. of NaN_3 and 2 eq. of Na_2CO_3 in dry DMSO at 130°C giving the product **XVI** with a high yield of 92% (Scheme VI) [44].

Transition metal-free 1,2,3-triazole synthesis

The reaction between the enamine substrate **XVII** and tosyl azide **XVIII** was examined under various circumstances. It has been investigated that the best medium for this reaction is DMSO as a solvent and $NaHCO_3$ as a base at a high temperature to provide the target product (5,6-dihydro-4*H*-imidazo[1,2-*c*][1,2,3] triazol-3-yl)(*p*-tolyl)methanone **XIX** with a significant yield (85%) (Scheme VII) [45].

Metal-free multicomponent reaction for the synthesis of 1,2,3-triazoles using phosphonium salts

Wu and his coworker have synthesized the target 4,5-disubstituted 1*H*-1,2,3-triazoles **XXII** through the reaction of (ethoxycarbonylmethyl) triphenylphosphonium bromide **XX**, benzaldehyde **XXI,** and NaN_3 in the presence of L-proline as a catalyst. It also was investigated that a high yield of the product (80%) was obtained when the mixture was stirred in DMSO solution at ambient temperature for 24 h (Scheme VIII) [46].

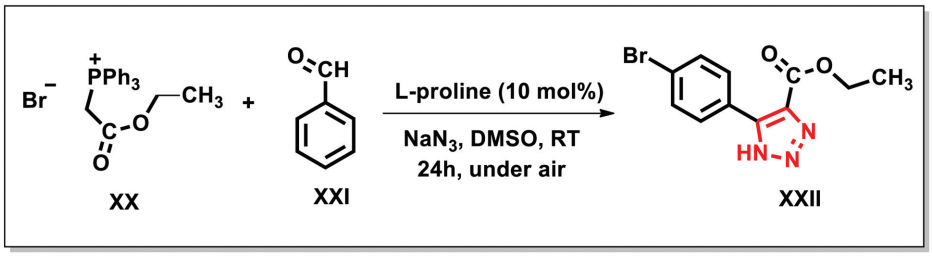
Metal-free mechanochemical synthesis of 1,2,3-triazole through organo-catalyzed oxidative azide-olefin cycloaddition

Under chemical conditions, the solution chemistry gives the main product associated with the byproduct. These conditions included high temperatures and long reaction times. In contrast, the mechanochemical condition generates the desired main product as well as preventing the formation of byproducts in a comparatively shorter time. With regard to yield, reaction time, and product specificity, mechanochemistry generally outperforms solution chemistry. As shown in Scheme IX, benzyl azide **XXIII** was mixed with nitro-olefin (3-(2-nitrovinyl)thiophene) **XXIV** in the presence of CTAB (cetyltrimethylammonium bromide), which is a quaternary ammonium surfactant and two stainless steel milling balls to give the desired product, 4-nitro-1*H*-1,2,3-triazole **XXV**, through the use of flash column chromatography on silica gel, a high-quality and purified product with a high yield (98%) [47].

Metal-free enamine annulation synthesis

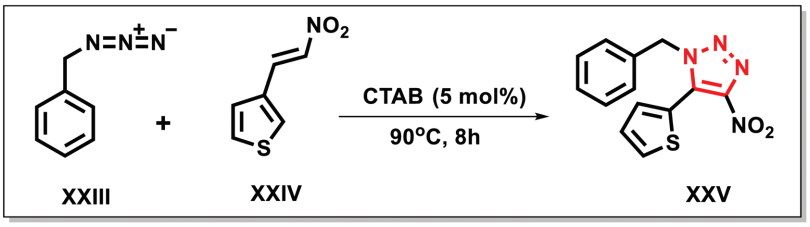
It has been reported that the reaction of the enaminoester **XXVI** with sulfonyl azide **XXVII** in the presence of TMEDA (tetramethyl ethylenediamine) as a base to promote the reaction

Scheme VIII



Metal-free synthesis of 4,5-disubstituted 1*H*-1,2,3-triazole **XXII**.

Scheme IX



Mechanochemical synthesis of 4-nitro-1*H*-1,2,3-triazole **XXV.**

and using water as a solvent produced a high-yield product (85%) of N^2-sulfonyl 1,2,3-triazole derivative **XXVIII** without using any metal reagents. Also, it was observed that this high yield was indicated by raising the temperature to 60°C and increasing the reaction time to 12 h (Scheme X) [48].

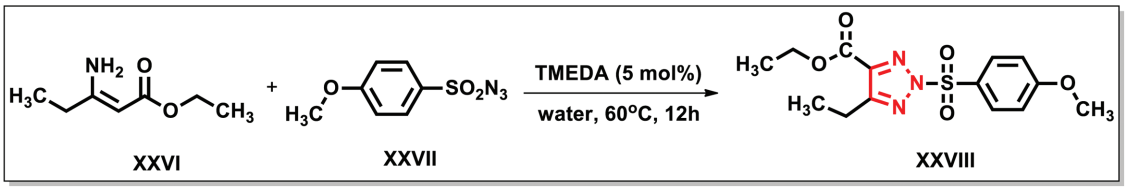
To discover more about the effect of the reaction medium on the reaction results, the reaction solvent was changed to DMSO with the same substrates, and N^2-H 1,2,3-triazole **XXIX** was obtained (Scheme XI) [48].

Metal-Free Regioselective Synthesis of functionalized 1,2,3-triazoles through 1,3-dipolar cycloaddition of alkanone enolates with azides in deep eutectic solvents

In this research, the 1,3-dipolar cycloaddition reaction of alkanone enolates with azides was carried out in the choline chloride/urea or choline acetate/urea eutectic mixture, and a metal-free procedure was established for the regioselective synthesis of densely functionalized 1,2,3-triazoles. This study is notable for its ability to combine enolate formation, click cycloaddition, reduction, and etherification reactions into a single one-pot technique that yields valuable pharmacologically active triazole derivatives, high regioselectivity, and reactions carried out under mild conditions (room temperature).

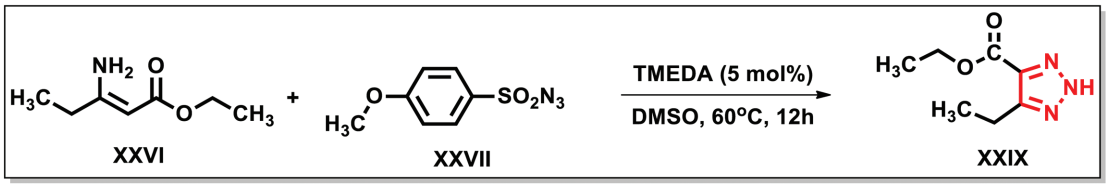
The experiment was started with the reaction of 1-phenylpropan-2-one **XXX** with t-BuOK (potassium tert-butoxide) for 1 h at RT (25°C) in choline chloride (ChCl)/urea (DES_1) to produce the enolate derivative **XXXI**. The latter compound was then reacted with 3-methoxy phenyl azide **XXXII** in choline acetate (ChOAc)/urea (DES_2) to give the target 1-(3-

Scheme X



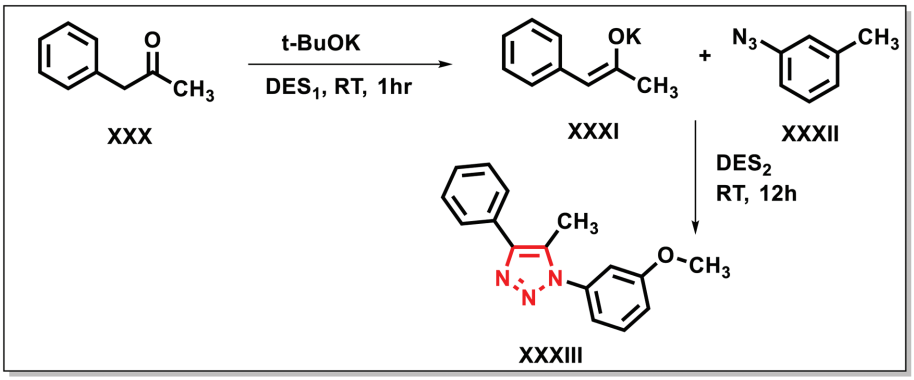
Amine-catalyzed synthesis of N^2-sulfonyl 1,2,3-triazole derivative **XXVIII**.

Scheme XI



Synthesis of N^2-sulfonyl 1,2,3-triazole derivative **XXIX** using DMSO as a solvent.

Scheme XII



1,3-Dipolar cycloaddition of alkanone enolates with azides in deep eutectic solvents to synthesize the functionalized 1,2,3-triazole derivative **XXXIII**.

methoxyphenyl)-5-methyl-4-phenyl-1*H*-1,2,3-triazole **XXXIII,** which was separated after 12 h. of the reaction time in a high yield (98%) (Scheme XII) [49].

Metal-free and azide-free synthesis of 1,2,3-triazoles

Due to the 1,2,3-triazoles' important drug-like properties, numerous researchers are searching for efficient novel synthesis techniques and found that metal and azide had an impact on the reactions. (i) Metal-free synthetic techniques are preferred to cut expenses for waste disposal and get rid of the possibility of residues of transition metals in manufactured products.

(ii) Azides are also unwanted intermediates for the industrial synthesis of 1,2,3-triazoles due to their toxicity and accompanied heat risks [50].

One-pot, metal-free, and azide-free synthesis of 1,2,3-triazoles from α-keto acetals and amines

By combining the three components in this reaction, α-keto acetal **XXXIV**, $TsNHNH_2$, and aniline **XXXV** together at room temperature in the presence of DMSO at the beginning of the reaction produced moderately greater yields of the desired 1,2,3-triazole **XXXVI** compared with the traditional successive synthesis of the *N*-tosylhydrazone at room temperature through the addition of the amine and then heating to 80°C. By adding MeMgBr to the desired 1,2,3-triazole **XXXVI** in THF at 0°C, 1,2,3-triazole derivative **XXXVII** was formed (Scheme XIII) [50].

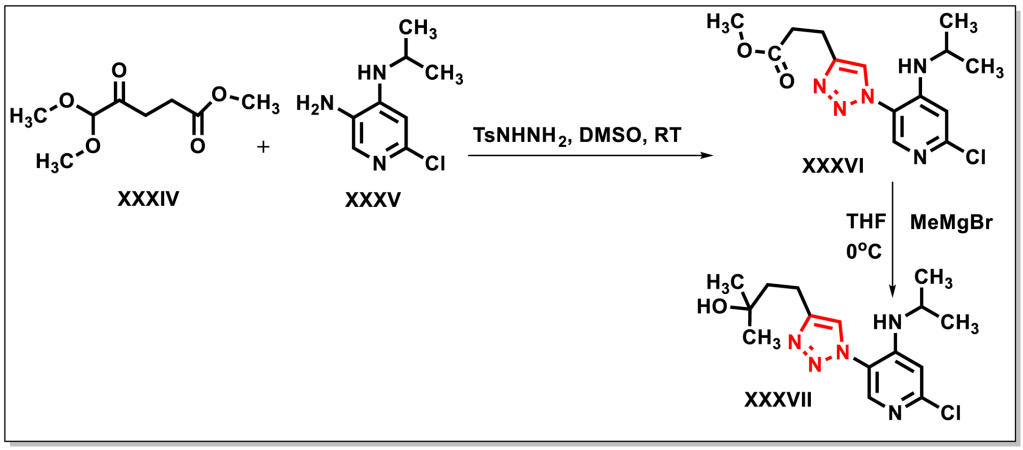
One-pot, metal-free, and azide-free synthesis of 1,2,3-triazoles through iodine-mediated C–N and N–N bond formation

This strategy was carried out using 4-methyl aniline **XXXVIII**, phenylacetylene **XXXIX,** and *N*-tosylhydrazine **XL** in DMSO as the best solvent and O_2 as a suitable oxidant with iodine at 120°C for 4 hrs in a one-pot manner giving the required product 1,4-disubstituted-1,2,3-triazole **XLI** with a high yield (89%) (Scheme XIV) [51].

Metal-free and Azide-free synthesis of 1-phenyl-1H-1,2,3-triazole through the one-pot Sakai–Clark method

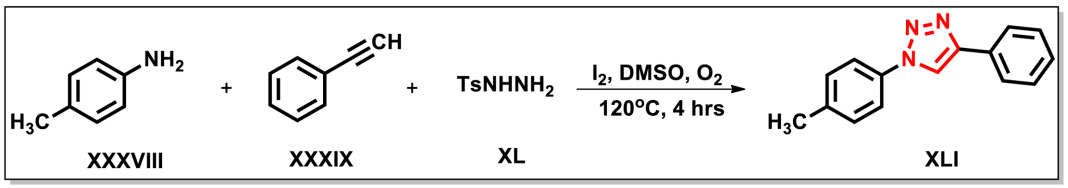
Developing the synthesis of 1,2,3-triazole by the Sakai-Clark method was carried out by the reaction of 2,4-dichloro-3-(trifluoromethyl) aniline **XLII** with α,α-dimethoxy tosylhydrazone **XLIII** and AcOH in the presence of THF (tetrahydrofuran) as a solvent with warming to 75°C for 5 h. gave 1-phenyl-1*H*-

Scheme XIII



Metal-azide-free synthesis of 1,2,3-triazole derivative **XXXVII**.

Scheme XIV



Metal-azide-free synthesis of 1,2,3-triazole derivative **XLI** through iodine-mediated one-pot reaction.

1,2,3-triazole **XLIV** in excellent efficiency and purity (Scheme XV). This method is metal-free and avoids the use of aryl azide to minimize the use of azides on a large scale due to its explosive features [52].

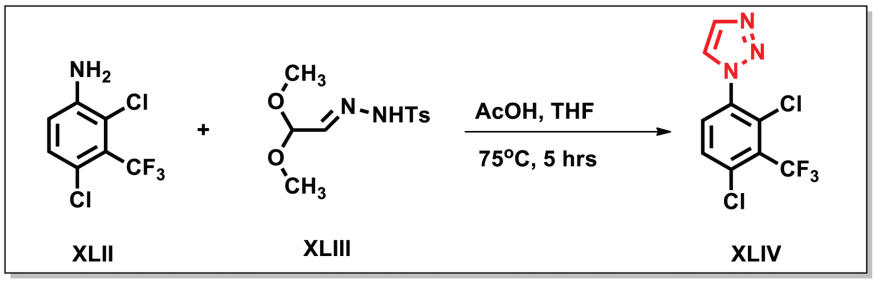
Metal-free and azide-free synthesis of 1,2,3-triazole from α,α-difluoro-N-tosylhydrazone and amine through the C-F Bond Cleavage

Fluorine-containing compounds have drawn interest because of their numerous applications in a variety of industries. They have a special reactivity that allows them to serve as reagents through the C-F bond cleavage. It has been reported that the reaction of α,α-difluoro-*N*-tosylhydrazone **XLV** with aryl amine (*p*-methyl aniline) **XLVI** using LiO^{t}Bu as the base in the presence of toluene at 100°C for 4 hrs led to the formation of the desired product 1,4-disubstituted-1,2,3-triazole **XLVII** in a high yield (99%) (Scheme XVI) [53].

Metal-free and azide-free synthesis of 1,4,5-trisubstituted-1,2,3-triazole via photoinduced multicomponent regioselective

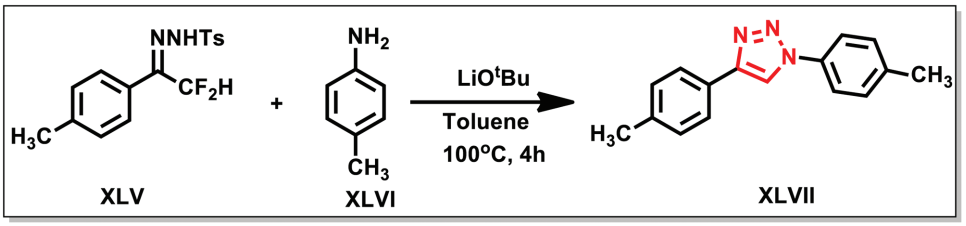
Marzi *et al.* have investigated that the reaction of 3-(phenylimino)indolin-2-one **XLVIII**, benzaldehyde **XLIX,** and tosylhydrazine **L** in the presence of Cs_2CO_3 (3 eq.) as an appropriate base in DMF as the most effective solvent at 100°C under sunlight for 6 hrs. provided the appropriate 1,4,5-trisubstituted-1,2,3-triazole derivative **LI** in a good yield (89%) (Scheme XVII). The same reaction was performed in the dark to examine how light may affect the reaction, and it was observed that a tiny quantity of the product was formed. The result showed that this reaction depends on light [54].

Scheme XV



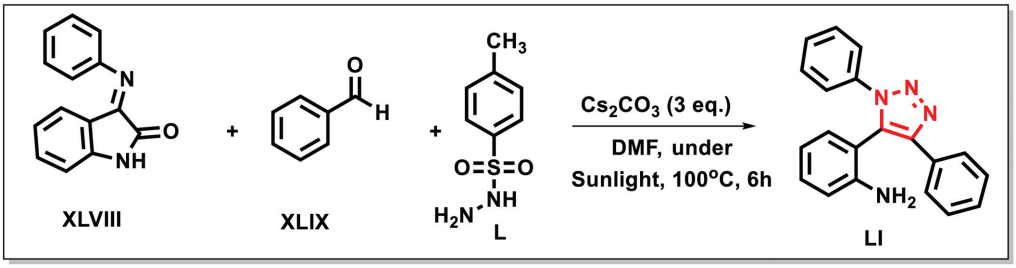
Metal-azide-free synthesis of 1-phenyl-1*H*-1,2,3-triazole through the Sakai-Clark method (one-pot reaction).

Scheme XVI



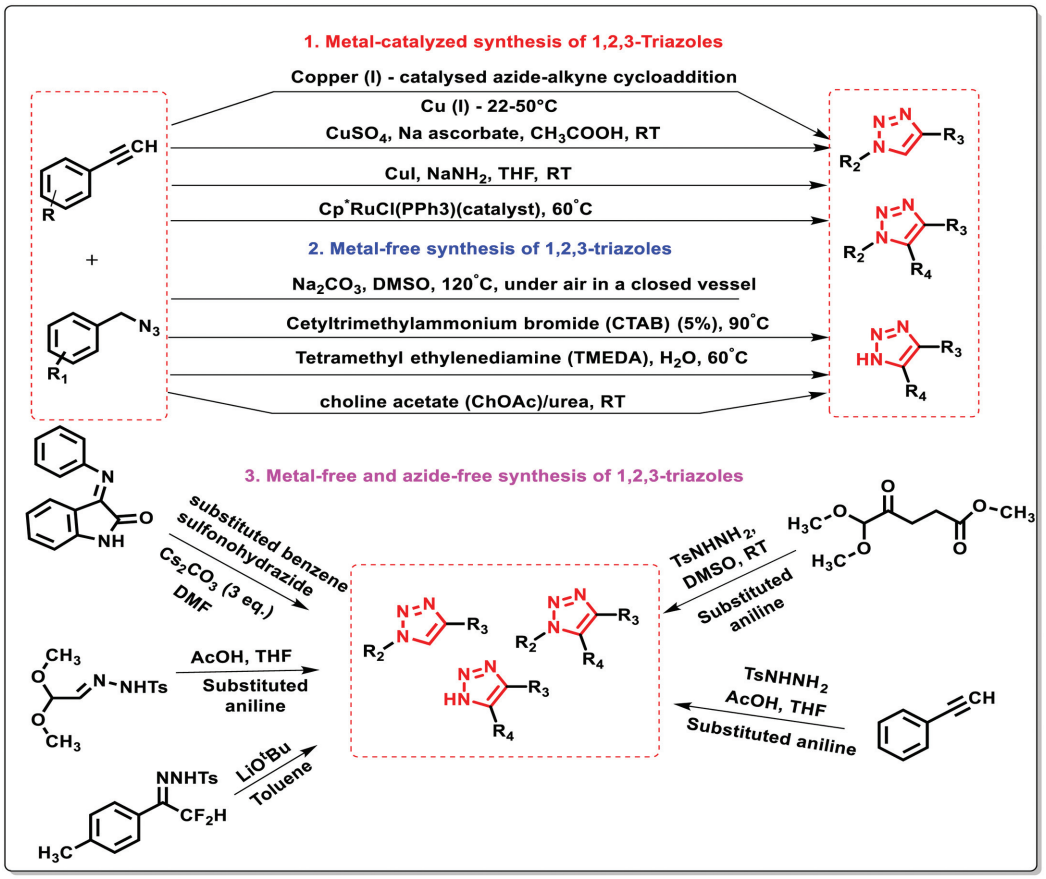
Metal-free and azide-free synthesis of 1,2,3-triazole derivative **XLVII**.

Scheme XVII



Metal-free and azide-free synthesis of 1,4,5-trisubtituted-1,2,3-triazole derivative **LI** under sunlight effect.

Scheme XVIII



A summary of various synthetic approaches toward the synthesis of 1,2,3-triazoles.

A summary of the different synthetic methodologies for the synthesis of 1,2,3-triazoles is elaborated in Scheme XVIII:

Biological activity of 1,2,3-triazole hybrid compounds

The 1,2,3-triazole moiety is a desirable prototype because it offers great stability even in severe oxidizing and reducing conditions. Its propensity to generate hydrogen bonds also makes it more soluble, which facilitates binding to biomolecular targets [55,56]. 1,2,3-Triazole derivatives have been found to exhibit a wide range of biological features through a variety of mechanisms, including enzymatic action and receptor-mediated mechanisms.

Anticancer activity

Cancer is an extremely serious health issue that affects people of all ages globally and is a major cause of mortality. Cancer refers to a group of diseases that are characterized by the abnormal growth and spread of cells that are not under control. There are around 277 different types of cancer disorders. Men are more likely to get liver, stomach, colon, prostate, and lung cancer than women, who are more likely to get breast, colorectal, lung, cervix, and stomach cancer [57].

Derivatized 1,2,3-triazoles have long been studied, mostly for their potential in cancer treatment. In-depth research has been done into this particular topic by many groups. Mallikanti *et al.* discovered a series of morpholine-linked 1,2,3-triazole compounds. When compared with the standard doxorubicin, which has an IC_{50} value of 7.50 µM, compound **8** (Fig. 4) showed exceptional efficacy with an IC_{50} value of 3.42 µM against the breast cancer MCF-7 cell line. SAR indicated that the electron-withdrawing property of the chloro-substituent on the phenyl ring has increased the cytotoxic activity of compound **8** [58].

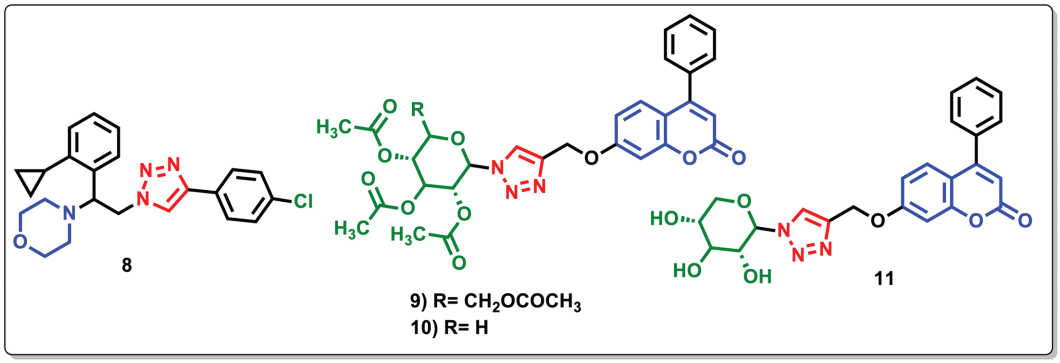
Numerous coumarin compounds are widely known for their powerful anticancer properties that result from inhibiting EGFR, VEGFR-2, or CDK-2 kinases. Also, heterocycle-glycoside hybrids are significant systems with a high level of biological interest. Glycosyl heterocyclic motif-based substances have shown a strong antitumor effect. As a result, El-

Sayed and colleagues developed and synthesized a novel set of triazole-coumarin-glycosyl hybrids with varying sugar portions using molecular hybridization to find anticancer drugs with significant activity. It has been found that compounds **9** and **10** have shown the best and greatest promise for cytotoxic activity against human pancreatic (Paca-2), melanoma (Mel-501), prostate (PC-3), and melanoma (A-375) cancer cell lines, while compound **11** only demonstrated promising activity against Mel-501 and A-375 cells [59]. The cytotoxicity of coumarin-triazoles **9** and **10** was confirmed by their binding to the CDK-2 active site, leading to CDK-2 inhibition [59]. The structure–activity relationship investigated on the coumarin-triazole scaffold showed that the cytotoxicity of compounds **9**, **10**, and **11** (Fig. 4) ranged from excellent to good potency. The acetylated compounds had exceptional potency, while the hydroxylated ones had moderate activity [59].

In addition, Veeranna *et al.* have developed and manufactured several 1,2,3-triazole derivatives hybridized with the indole scaffold. This study investigated that both compounds **12** and **13** (Fig. 5) showed strong anticancer efficacy against human hepatocellular carcinoma cells (HepG2) and human breast cancer cells (MCF-7) compared with doxorubicin [60]. SAR study showed that the *p*-hydroxyl substitution and the *m*-acetyl substitution of the phenyl ring as compounds **12** and **13**, respectively, led to noticeable anticancer activity [60].

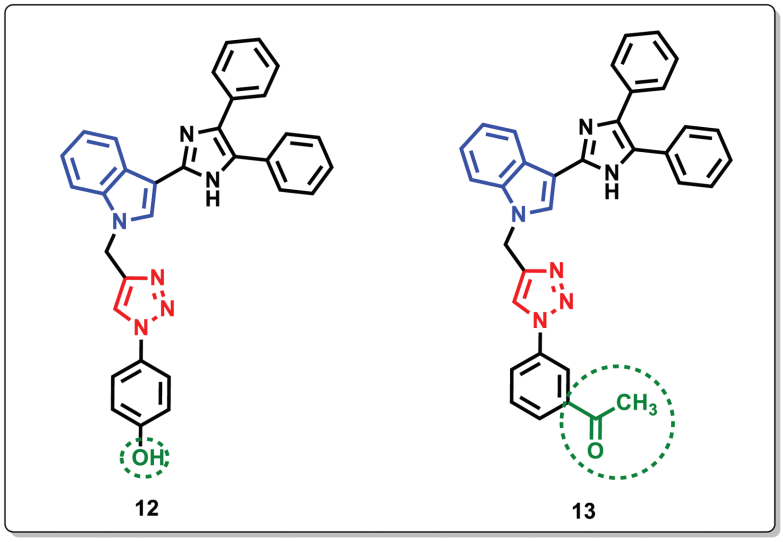
Also, the analog 3-(4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzo[d]isoxazole (PTB) **14** (Fig. 6) was found to be a potent antiproliferative agent against MV4-11 cells with an IC_{50} value of 2 µM. Molecular docking analysis of **14** with the second deacetylase domain of HDAC6 showed remarkable affinity, as the shape of **14** complemented with the binding site

Figure 4



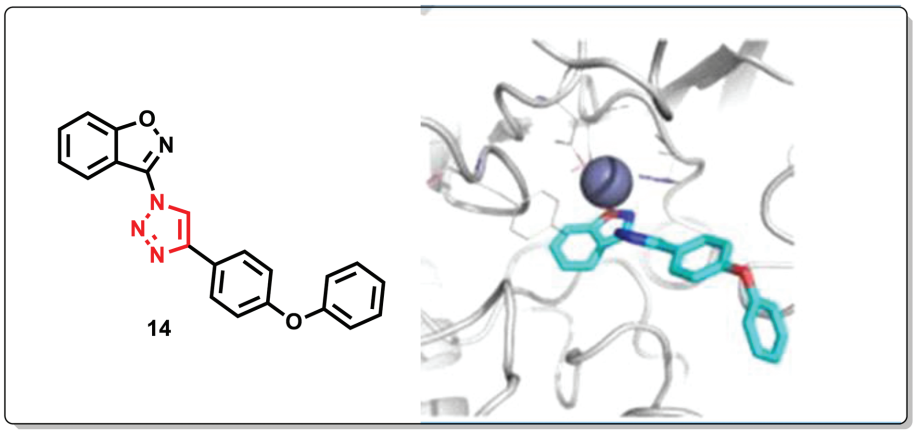
Examples of morpholine-1,2,3-triazole and coumarin-1,2,3-triazole-glycosyl hybrids as anticancer agents.

Figure 5



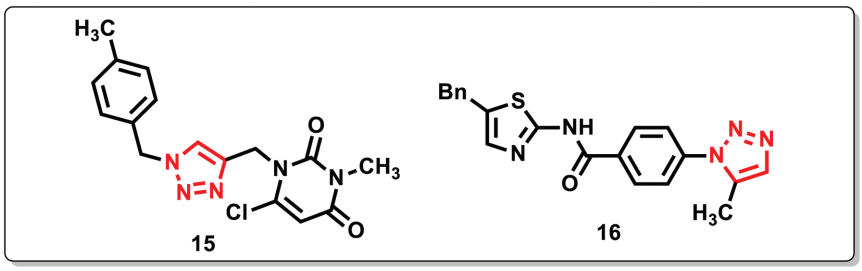
1,2,3-triazole-tethered indole hybrids as an anticancer agent.

Figure 6



The expected interaction form of compound **14** with the HDAC6 active site [61].

Figure 7



Representative 1,2,3-triazoles as effective anticancer agents.

of the enzyme. This leads to the creation of numerous molecular interactions within the hydrophobic region, accompanied by the formation of a hydrogen bond with the phenol side chain of Tyr-782 [61] as illustrated in Fig. 6.

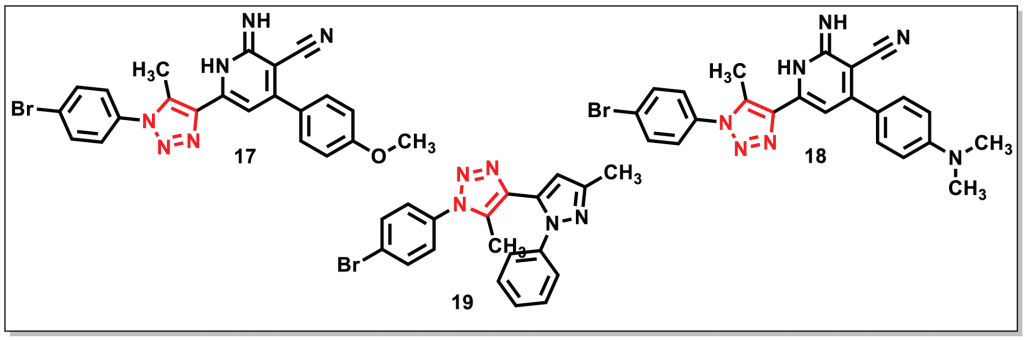
Also, Reddy *et al.* have designed and synthesized the 1,2,3-triazole derivative **15**, which exhibited more growth inhibition action against HeLa and HUH-7 tumor cell lines than the positive control, 5-fluorouracil (5-FU), with IC_{50} values of 4.5 and 7.7 M, respectively (Fig. 7) [62].

In another research, Pokhodylo and coworker synthesized 1,2,4-thiadiazole and 1,3-thiazole derivatives of 1,2,3-triazoles, which were tested at a concentration of 10^{-5}M in a primary anticancer assay against 60 cell lines. Compound **16** demonstrated noteworthy efficacy against both the K-562 leukemia cell line (with a growth percentage, or GP, of 21.47%) and the SK-MEL-5 melanoma cell line (with a GP of 23.91%) (Fig. 7) [63].

Recently, Yasmin *et al.* have created and produced 1,2,3-triazole derivatives and established that the 2-iminopyridine congeners **17** and **18** elicited the most effective antiproliferative effects in comparison with 5-fluorouracil against human breast adenocarcinoma (MCF-7) (Fig. 8**)**. The dimethylamino phenyl-2-imino-pyridine derivative **18** seemed to be 1.4 times more potent than the standard drug, with IC_{50} values of 3.9±2.3 and 5.6±0.89 μM, respectively. In addition, the cytotoxic activity of the other analog, p-methoxyphenyl-2-imino-pyridine **17**, was comparable to that of 5-fluorouracil, with an IC_{50} value of 5.2±2.1 μM. Moreover, MCF-7 cancer cells produced a sensitivity against the pyrazole derivative **19** similar to that against the reference drug (IC_{50}; 5.8 ±5.0 μM) (Fig. 8**)**.

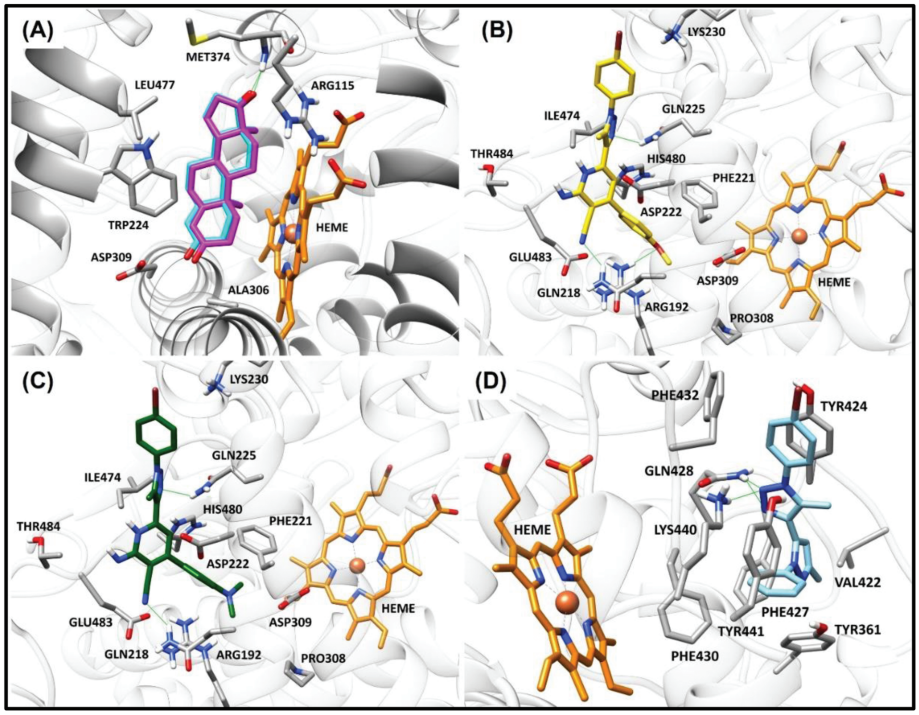
The molecular docking results of compounds **17** and **18** showed good binding affinity to allosteric site 1 of aromatase enzyme, while compound **19** revealed good binding affinity to allosteric site 2 of the same enzyme and the formation of three hydrogen

Figure 8



The most promising antiproliferative 1,2,3-triazole derivatives against the MCF-7 cell line.

Figure 9



Molecular docking results of the strongest compounds **17**, **18,** and **19** against aromatase enzyme.

bonds between the triazole N of the compound and both the NH_2 of GLN428 and the NH_3^+ of LYS440 (Fig. 9**).**

Antimicrobial activity

Antifungal activity

One of the most varied organisms on the planet is the fungus. Developing new fungicidal medications that have a high selectivity for fungal receptors and low affinity for human receptors is vital. This is because both humans and eukaryotes have numerous potential drug-receptor targets.

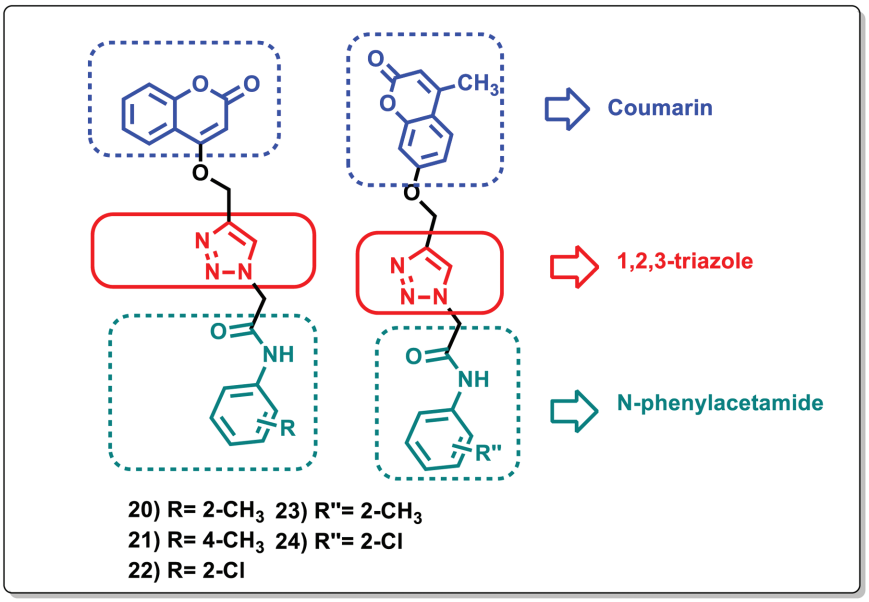
Fungal infections are on the rise nowadays and kill 1-2 million people a year. Approximately 90% of the fatalities are attributed to the Aspergillus and Candida species. In recent years, 1,2,3-triazole compounds have been developed and tested for antifungal activity, with some potential action against various fungi [1].

A number of novel 1,2,3-triazole-tethered coumarin hybrids that were joined by *N*-phenyl acetamide (Fig. 10) were successfully and efficiently produced [1]. *Candida albicans*, *Fusarium oxysporum*, *Aspergillus niger*, *Cryptococcus neoformans*, and *Aspergillus flavus* were all the targets of an investigation into the antifungal impact. When compared with miconazole, compounds **20**, **21**, **22**, **23**, and **24** displayed significant antifungal activity (Fig. 10).

By studying the structure–activity relationship (SAR) of the previous compounds, it was clear that compounds **20** and **21** which have a methyl group at the ortho and para positions of the phenyl ring, respectively, and compound **22** which has a Cl group at the ortho position, showed potency against all the fungal strains that were equal to or double that of miconazole. Also having CH_3 and Cl groups in the ortho position of the phenyl ring, compounds **23** and **24** demonstrated excellent antifungal activity against all fungal strains [64]. This might be explained by the fact that the increase in lipophilicity increases the target activity.

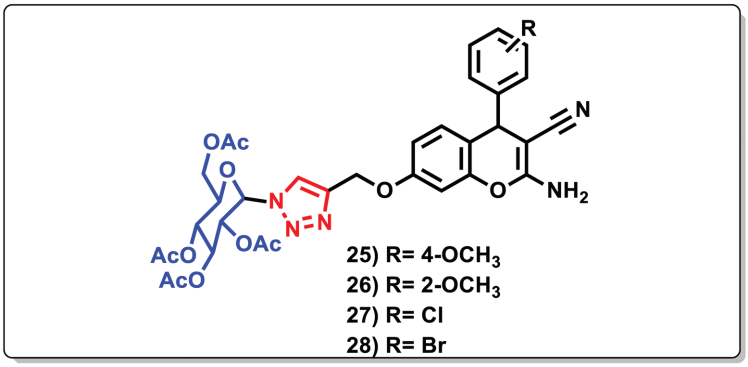
Using click chemistry, Thanh and coworkers have synthesized 1*H*-1,2,3-triazole-tethered 4*H*-chromene-D-glucose conjugates of tetra-*O*-acetyl-*b*-D-glucopyranosyl azide and propargyl ethers. Antifungal evaluations were performed for the previous derivatives on *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans,* and *Saccharomyces cerevisiae*. Standard medications included Miconazole and Fluconazole. It was investigated that compound **26** was more active than the standard drugs against *A. niger* with MIC (1.56 µM). Compound **25** was more effective than miconazole against *C. albicans* but less effective than fluconazole, whereas compounds **27** and **28** were more effective than miconazole against *S. cerevisiae* (Fig. 11**)** [65]. SAR showed that the triazoles carrying monomethoxy-substituted phenyl ring **25** and **26** have moderate to most active O-CH3 of these triazoles [65].

Figure 10



N-phenylacetamide-linked 1,2,3-triazole-coumarin-conjugated chemical structures possessing high antifungal activity.

Figure 11



1*H*-1,2,3-triazole-tethered 4H chromene-D-glucose conjugates chemical structures possessing high antifungal activity.

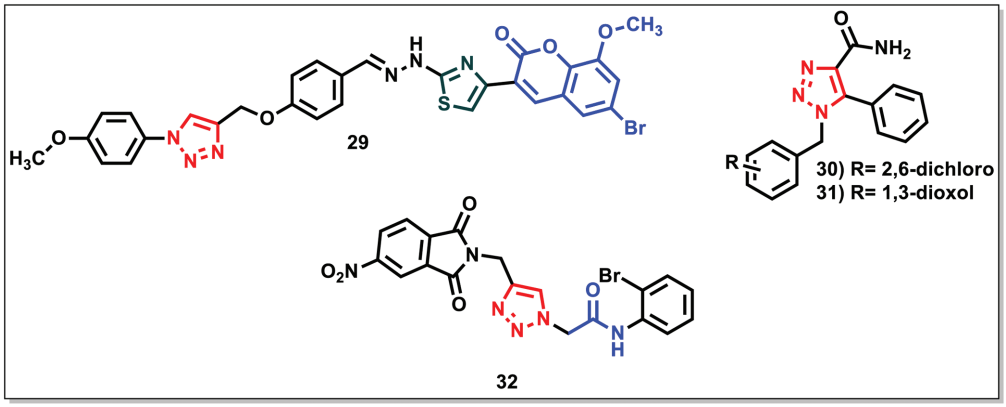
A series of triazole–thiazole conjugates were created by Gondru *et al.* using a multicomponent reaction strategy. The results revealed that when compared with the standard miconazole (MIC, 18.7 µM), the 6-bromo-8-methoxycoumarinyl group-derived compound **29** (MIC, 5.9 µM) was discovered to be a highly effective hybrid of the studied series against the majority of Candida spp. (Fig. 12) [66].

Gonzalez-Calder *et al.* have synthesized different benzylic 1, 2, 3-triazole-4-carboxamides using the one-pot technique with respectable yields. The antifungal activity of the sequence of compounds was assessed *in vitro* against four filamentous fungi and four species of *Candida*.

It was demonstrated that the most effective antifungal agents (of all the experimental compounds) against *R. oryzae* were compounds **30** and **31** with an MIC value of 0.017 µM (Fig. 12**)**, which outperformed the standard drug itraconazole with an MIC of 0.14 µM [67]. The structure–activity relationship indicated that the 4-phenyl-4-carboxamide triazole moiety was in charge of the antifungal effect, regardless of whether it was in the electron-poor ring **30** or the electron-rich ring **31**. Because R. oryzae causes infections in immunocompromised patients that can result in mucormycosis, the antifungal action of **30** and **31** against this organism is quite valuable [67].

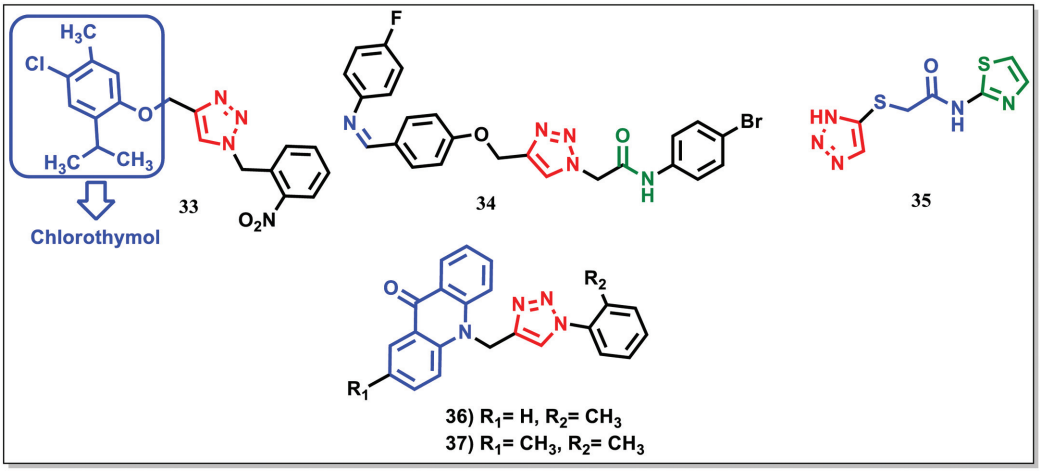
In another research, Mori and colleagues conducted a study where they created and produced a range of compounds that consisted of amide-containing phthalimide with 1H-1,2,3-triazole derivatives. These newly synthesized compounds were then examined for their potential antifungal properties against the Candida albicans fungus. Out of all the tested compounds, compound **32** (Fig.12) displayed the highest effectiveness as an antifungal candidate, exhibiting a growth inhibition rate of 17.56% at a

Figure 12



Chemical structures of 1,2,3- triazole-based derivatives of antifungal activity.

Figure 13



Models of 1,2,3-triazole – established compounds as a potent antibacterial agents.

concentration of 65.94 μmol/mL. The structure–activity relationship analysis indicated that the addition of a bromine substitute with higher electronegativity in the ortho position of the phenyl ring led to an increase in activity. However, the potency decreased when chlorine or fluorine substitutions were introduced [68].

Antibacterial activity

Even though there are many antimicrobial medicines available, microbial infections are the leading cause of death globally. Global health security is at risk due to the potential emergence of microbial resistance, which could be the next major health emergency, especially considering the ongoing Covid-19 pandemic [69]. According to the GARDP annual report, 1.2 million individuals per year die from diseases brought on by drug-resistant bacteria [70]. To develop antimicrobial therapies that will protect people from future health problems, scientists are applying a variety of strategies. The molecular hybridization strategy has emerged as the most viable approach to accomplish this goal.

In a recent research, it was proposed that introducing a 1,2,3-triazole moiety to thymol can enhance its water solubility and improve its biological potency as thymol exhibits poor physicochemical characteristics, such as limited water solubility, a high rate of sublimation, and a high incidence of photoreactivity. In addition, a recent research demonstrated that the thymol hydroxyl functional group was essential for its antibacterial efficacy. Thymol's hydroxyl group makes it a great candidate for structural transformation by the addition of a triazole group. It was shown that compound **33** (Fig. 13) displayed the highest mean zone of inhibition against methicillin-resistant *S. aureus* (MRSA), measuring 38.7 mm and 24.7 mm at concentrations of 100 μg/ml and 10 μg/ml, respectively, as opposed to 30.0 mm for the standard medication, 10 μg ampicillin disc (OXOID). This compound can be effectively compared with the standard medication (ampicillin) in the treatment of infections brought on by staphylococci and other studied bacterial strains. When compared with the parent molecule, thymol, compound **33** is around 3–15 times more powerful, with mean zones of inhibition of 11.0 and 1.7 mm, respectively [71]. Structure–activity relationships revealed that chlorine substitutions at the carbon-4 positions of the thymol nucleus were crucial in giving compound **33** a higher activity than that of its parent chemical, thymol. Also, the hydroxyl group on thymol provides an activity as well, as thymol demonstrated a mean zone of inhibition against all bacteria with a mean zone of inhibition ranging between 13.7 and 2.7 mm, supporting earlier findings that the hydroxyl group is essential for thymol's antimicrobial effect [71].

Moreover, it was intended to synthesize certain derivatives containing imine-1,2,3-triazole and amide-1,2,3-triazole units for antimicrobial testing, drawing inspiration from their bioactivity profiles [72]. Among the imine-linked 1,2,3-triazole compounds, compound **34** exhibited excellent performance as an antimicrobial candidate and greater efficacy when compared with ciprofloxacin, with an MIC value of 0.0094 μmol/mL against *S. aureus* as a Gram-positive bacterium and an MIC of 0.0061 μmol/mL against the two Gram-negative bacterial strains *S. enterica* and *P. aeruginosa* (Fig. 13) [72]. Following SAR analysis, it was discovered that the majority of the synthesized imine-based 1,2,3-triazole hybrids were more effective than their corresponding terminal alkynes, supporting the idea that molecular hybridization increased the activity. Triazoles are shown to be more effective against Gram-positive bacteria when they have a bromine atom on the phenyl ring. It was discovered that compound **34**, which has a bromine atom on the phenyl ring, was the most effective against *S. aureus* [72].

In addition, the researchers planned to discover new medications with unique mechanisms of action to treat resistant infections caused by the Gram-negative bacteria *E. coli*. Using a metabolically biased high-throughput screen against *E. coli* K12 in the search for new antifolates, a hit series of thioacetamide-triazoles was discovered. It has been shown that the cysteine synthase A (CysK) enzyme activates these compounds, enabling them to act as prodrugs. In addition to playing a critical role in the biosynthesis of cysteine and the assimilation of sulfur, homocysteine, a byproduct of CysK, is another link to the folate biosynthetic pathway. Thioacetamide triazoles (TATs) prevent the growth of *E. coli* by forming a synthetic product with the CysK substrate *O*-acetyl-L-serine. Compound **35** (Fig. 13) showed enhanced solubility, plasma stability, and metabolic stability with the best MIC values (≤3.1 μg/mL) [73].

SAR of compound **35** showed that triazole NH is crucial for the triggering of CysK and the associated generation of false products. It was found that 1,2,3-triazoles is better than 1,2,4-triazoles. The pharmacological activities were improved by the addition of the thiazole heteroaryl system. In the

thioacetamide group, methylene linker n=1 is optimal, and methyl branching loses the activity; *N*-methyl or ethyl groups decrease the activity; sulfur substitution is required for the activity; and reversal or removal of the amido group decreases the activity [73].

Aarjane and colleagues have recently developed and manufactured a fresh category of 1,2,3-triazole derivatives that incorporate acridone. They conducted tests using these derivatives against various bacteria, including Staphylococcus aureus (a Gram-positive bacterium), Pseudomonas putida, Klebsiella pneumonia, and Escherichia coli (all Gram-negative bacteria). In addition, they examined the structure–activity relationship of certain potent compounds to gain a better understanding of their effectiveness. The results revealed that S. aureus displayed the highest sensitivity to the synthesized compounds. In addition, the SAR findings suggest that incorporating a 1,2,3-triazole ring leads to improved antibacterial activities against all bacteria that were tested. Examining the impact of substituents on the phenyl group of the acridone-1,2,3-triazole scaffold, it was observed that compounds with an o-methylphenyl group **36** and **37** (Fig. 13) exhibited the most effective antibacterial activity against S. aureus, displaying a minimum inhibitory concentration (MIC) of 10.11 and 12.31 g/mL, respectively [74].

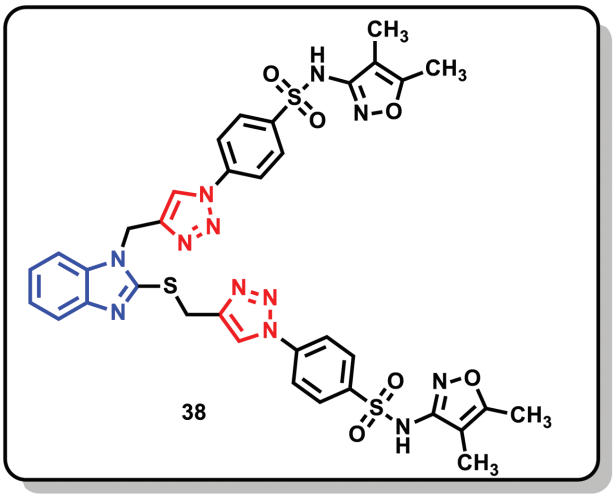
Antiviral activity

The SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) and its variations, particularly the Omicron type, continue to pose a serious hazard to human health. The need for powerful drugs that could combat the SARS-CoV-2 viral pandemic and newly emerging mutations is growing. From either benzimidazole or isatin precursors, a family of 1,2,3-triazoles was created, as 1,2,3-triazoles have a broad range of variable actions, making them pharmacologically interesting scaffolds. In the case of 1-benzyl-1*H*-1,2,3-triazoles-carbohydrate molecular conjugates, it was discovered that one compound had a larger cytotoxic impact and selectivity index (SI) than azidothymidine, zalcitabine, and didanosine (the reference drugs) [75].

In this research, most of the studied compounds showed good binding results against the SARS-CoV-2 and Omicron spike proteins, in comparison to the reference medications, according to molecular docking studies and in vitro enzyme activity. Compound **38** (Fig. 14) especially had the highest *in vitro* affinity against the Omicron spike protein and the SARS-CoV-2 spike protein, with IC_{50} values of 75.98 nM and 74.51 nM, respectively, for each protein [75]. The research showed that compound **38** efficiently inhibited SARS-CoV-2 with a great selectivity index (SI), demonstrating the drug's safety and suitability for use in the future and its evaluation in an animal model. Triazoles produced the steadiest molecule with the spike protein due to their reduced free energy. These interactions are hypothesized to alter the shape of the structural proteins of the virus, obstructing access to host cells and, as a result, limiting viral replication and infection [75]. These results demonstrated that compound **38** has antiviral action and decreases inflammation caused by SARS-CoV-2.

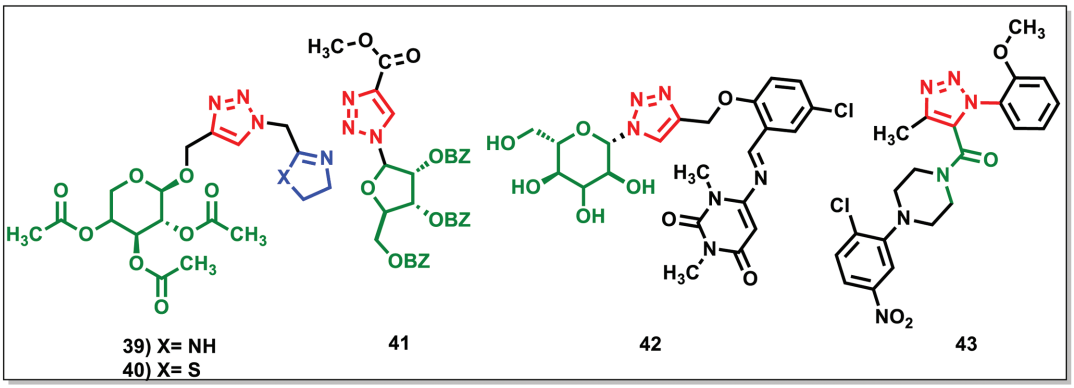
Humans are susceptible to the extremely contagious acute respiratory infection caused by the influenza A virus (IAV), which has a considerable impact on morbidity and mortality [76]. Influenza A virus is a threat to public health for which there are presently ineffective vaccines [76]. Neuraminidase inhibitors (NAIs) (peramivir, zanamivir, and oseltamivir phosphate), M2 ion channel blockers (amantadine and rimantadine), and RNA polymerase inhibitors (Xofluza and favipiravir) are currently available commercially as antiviral drugs to treat IAV. As a surface glycoprotein, the neuraminidase glycoprotein (NA) continues to be the most desirable target for anti-influenza therapies. It has been found that the estimated synthesis of a functionalized 1,2,3-triazole core is a property that is significant because this motif is present in several compounds that have been claimed to have anti-HIV properties. Small heterocyclic ring-containing compounds like imidazole, oxazole, and

Figure 14



The chemical structure of benzimidazole-1,2,3-triazole compound **38** as an SARS-CoV-2 inhibitor.

Figure 15



Examples of 1,2,3-triazole-based nucleosides and 1,2,3-triazole carboxamide derivatives as antiviral candidates.

thiazole have attracted a lot of attention in studies looking for new antiviral drugs. Therefore, Kutkat *et al.* have synthesized a new series of nucleosides carrying two hetero molecules. Antiviral studies have shown that compounds **39** and **40** were more active than oseltamivir and zanamivir against the H1N1 virus and demonstrated promising antiviral effectiveness against $H5N1_{wild}$, $H5N1_{V116A}$, and $H5N1_{N295S}$ (Fig. 15**)**. Both **39** and **40** displayed antiviral activity and safety profiles that were superior to oseltamivir *in vivo* and were comparable to zanamivir's [77].

Click chemistry was used to successfully produce new nucleosides of the ribavirin derived from 1,2,3-triazoles analogs shown in Fig. 15. With regard to HIV-1 RT (reverse transcriptase) activity and antiviral activity against influenza A replication, compound **41** was discovered to be superior to ribavirin with IC_{50} values 14 and 3.8 µM for influenza A and HIV-1 RT, respectively [78].

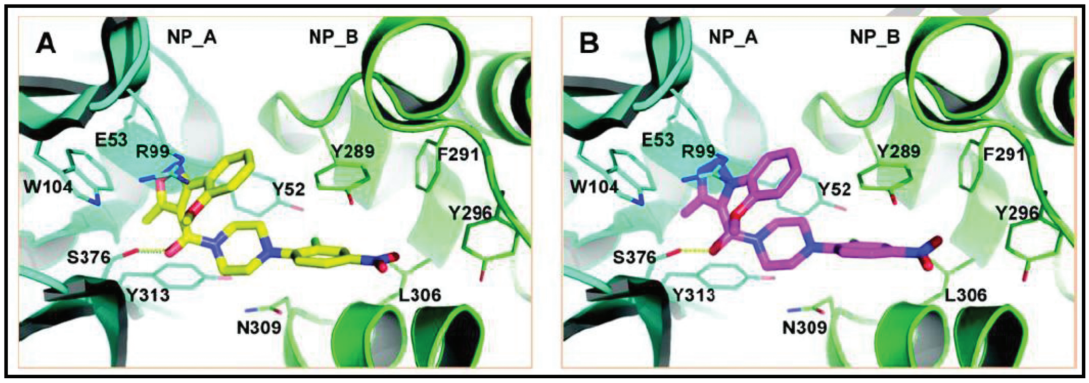
Research into how medications interact with DNA is crucial for the estimation of the molecular basis of drug action and, in particular, for the development of specific DNA-targeted therapies, of which antiviral agents are one. Researchers designed and synthesized sugar-imine derivatives appended with uracil and [1,2,3-triazole], and studied their binding to DNA. Docking investigations demonstrated that all compounds may engage CT-DNA through groove binding, especially compound **42** (Fig. 15) [79].

Also, a group of anti-influenza A compounds were developed and synthesized, which consist of 1*H*-1,2,3-triazole-4-carboxamide derivatives. Compound **43** significantly suppressed the replication of H_5N_1 (RG14), amantadine-resistant A/WSN/33 (H_1N_1), and oseltamivir-resistant A/WSN/1933 (H_1N_1, 274Y) viral strains (IC_{50}; 0.5–4.6 µM). According to molecular docking experiments, compound **43** interacts with nucleoprotein in a manner that is comparable to how nucleozin performs. (Fig. 16).

Antitubercular activity

Despite the availability of TB medications, 8.7 million people contracted the disease in 2011, and 1.4 million

Figure 16

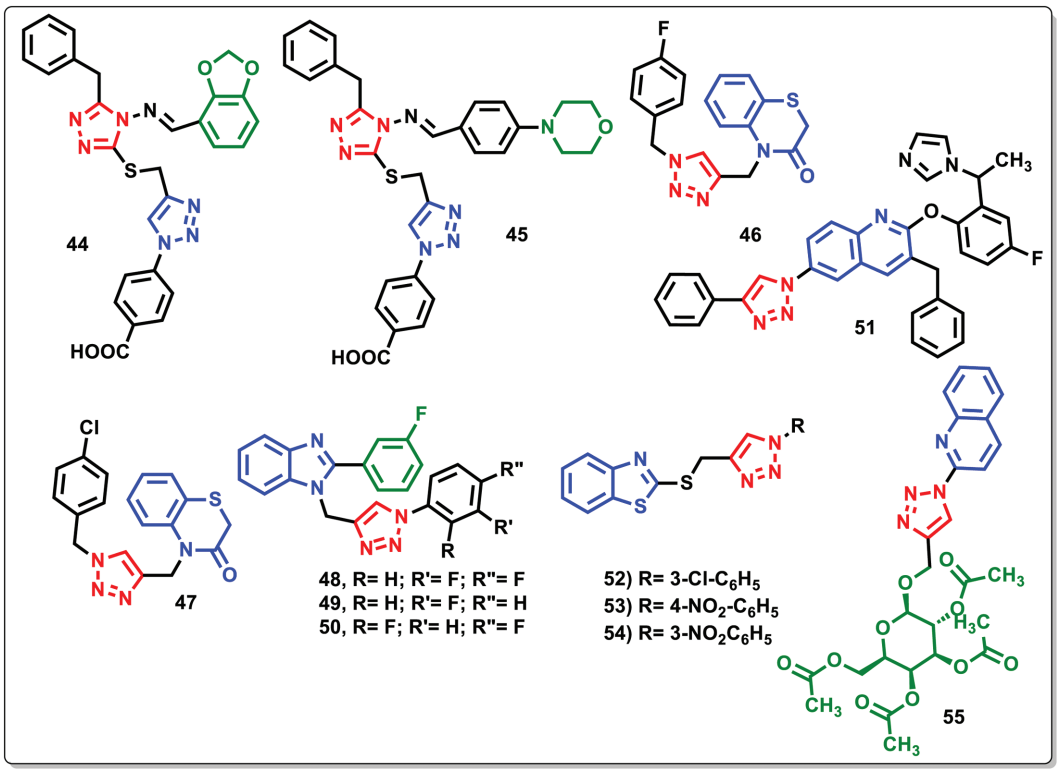


(A) Nucelozin and nucleoprotein complex structure and (B) Analog **43** and nucleoprotein compound structure [80].

died from it (recent WHO statistics). Threats to public health are posed by the rising incidence of TB strains that are multidrug resistant (MDR) and highly drug-resistant (XDR). The main causes of drug resistance for TB treatments are patient nonadherence, bad drug prescriptions, or inadequate medications [81]. InhA, a type II fatty acid synthase 2-trans enoyl-acyl carrier protein (ACP) reductase, is necessary for the formation of mycolic acid. The primary objective of the potent and famous antitubercular medication is isoniazid, according to a series of studies (INH) [81]. Finding new lead structures that could be helpful in the development of creative antitubercular medicines was the goal of the researchers. A new family of 1,2,3- and 1,2,4-triazole hybrid compounds was developed [82]. The InhA enzyme was evaluated *in vitro* using the proposed compounds. The InhA enzyme was completely (100%) inhibited by inhibitors **44** and **45** (Fig. 17) at a concentration of 10 nM. Various concentrations were used to calculate IC_{50} values. Compounds **44** and **45** were the most potential InhA inhibitors, with IC_{50} values of 0.074 and 0.13 nM when compared with the known IC_{50} of rifampicin and isoniazid, which were reported as 0.8 nM and 54.6 nM, respectively [82]. A series of 1,2,3-triazoles based on benzothiazinone were successfully created utilizing the click chemistry approach in the search for new potent compounds against M. tuberculosis (MTB) H37Ra and M. bovis BCG. Compounds **46** and **47** were found to be the most active compounds against MTB and M. *bovis* BCG characterized by lower MIC values (27.34-29.37 µg/ml) [83]. Furthermore, new derivatives of 1,2,3-triazole with fluorine-substituted benzimidazole units attached were synthesized and estimated as H37Rv strain inhibitors. In comparison to the standard rifampicin, compounds **48–50** showed superior activity. According to SAR analyses, the fluorine's highly electronegative component or the existence of a 1,2,3-triazole ring linked to the benzimidazole may be the cause of the fluorine's potential antimycobacterial activity (Fig. 17) [84].

In addition, different compounds bearing quinoline nucleus conjugated with triazolo, ureido, and thioureido substituents were synthesized by Upadhyaya *et al.* for demonstration of their antimycobacterial action. Compound **51** suppressed *M. tuberculosis* H37Rv up to 96% based on 1,2,3-triazole modification at an MIC value of 3.125 µg/ml. According to molecular docking evaluations, the polar functional groups of the antimycobacterial compound **51** and the amino acids of bacterial ATP-synthase interact through hydrogen bonds and electrostatic interactions [85].

Figure 17



Some examples of 1,2,3-triazole derivatives that have demonstrated antitubercular activity.

Furthermore, Mir and colleagues have synthesized 1,2,3-triazole conjugates of 2-mercaptobenzothiazoles and tested them for their antitubercular activity against the M. tuberculosis H37Rv strain. The obtained results showed that compounds **52–54** were potent analogs and suppressed the growth of previously mentioned strain at a concentration of 8 µg/mL (Fig. 17) [86].

In addition, various compounds bearing quinoline coupled with 1,2,3-triazole ring have also been produced in good yields using click chemistry. To determine their antitubercular efficacy against M. tuberculosis H37Rv, all of the derivatives were subjected to a luciferase reporter phage (LRP) assay. Quinoline-linked triazole sugar hybrid number **55** was discovered to be the most effective substance in the series, reducing the mycobacterium by 76.41% and 78.37% at concentrations of 5 and 25 µg/ml, respectively (Fig. 17) [87].

Antileishmanial and antitrypanosomal activity

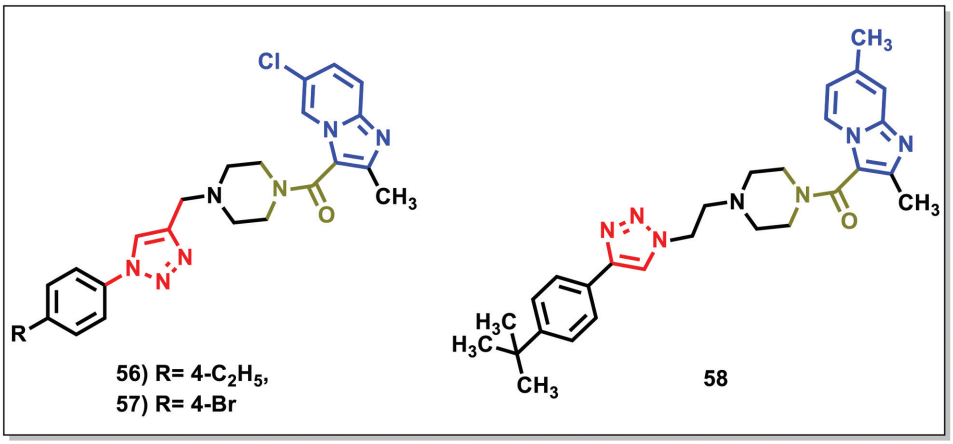
According to the WHO, one of the most ignored tropical diseases is leishmaniasis. Ninety distinct sandfly species are involved in the disease's transmission to its mammalian host, which is brought on by more than 20 different species of protozoan parasites. Treatment for leishmaniasis is difficult for those who have the infection, and it is even riskier and more difficult for those who are immunosuppressed and also coinfected with HIV [88].

Trypanosoma brucei, a protozoan parasite that affects people and is spread to them through the bite of a blood-sucking tsetse fly, is the cause of the neglected tropical disease (NTD) known as human African trypanosomiasis (HAT), also known as sleeping sickness. There is a need for additional clinical research to discover novel antitrypanosomal medications because the medications now used to treat HAT are ineffective against all stages and subspecies of the parasite [89].

Also, Trypanosoma cruzi, a member of the Trypanosomatidae family of protozoa, is the causative agent of the neglected tropical disease known as Chagas disease or American Trypanosomiasis. There are still between 6 and 8 million infected people in the world, which is a significant public health issue. The disease is widespread in Latin American nations, having a significant negative social and economic impact on people living there [90].

In this study, a novel series of 1,2,3-triazole analogs of imidazo-[1,2-a]-pyridine-3-carboxamides were designed and synthesized by the researchers. *In vitro* testing was conducted to determine the antileishmanial and antitrypanosomal activity of all synthesized and characterized compounds against Leishmania major and Trypanosoma brucei parasites, respectively. The three compounds **56**, **57,** and **58** (Fig. 18) had IC_{50} values that ranged from 15 to 47 µM and significantly inhibited the growth of promastigote forms of *L. major*. The most prominently active molecule **58** displayed a similar IC_{50} value (15.1 µM) to that of the reference drug, Miltefosine (12.6 µM). The relationship between the structure of compounds **56** and **57** and their activity level revealed that the presence of electron-withdrawing groups, particularly positioned at the para position of the phenyl group connected to the triazole nucleus, had a positive effect on their antileishmanial potency. When these interactions between the co-crystal ligand and the target protein

Figure 18

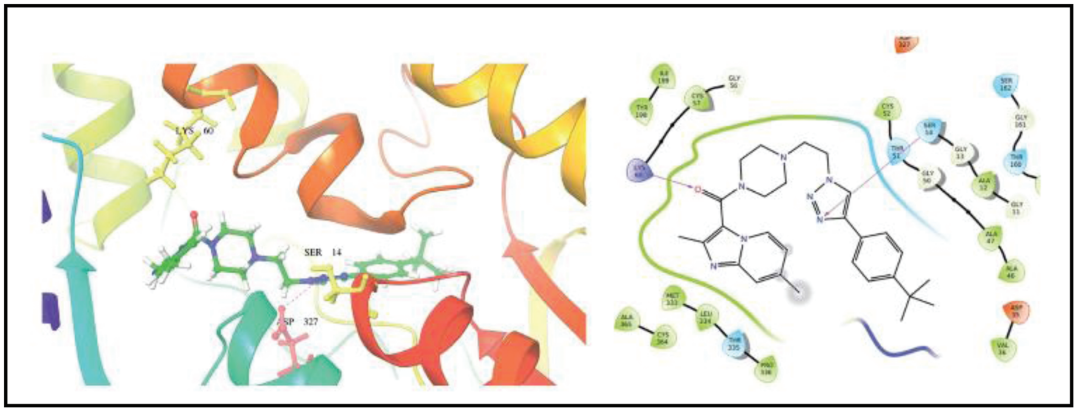


The most promising compounds bearing 1,2,3-triazole as antileishmanial agents.

are rigorously analyzed, it was shown that the identical amino acid residues (SER14, LYS60) are involved in the same kind of hydrogen bond interactions with both the co-crystal ligand and compound **58** (Fig. 19) [88].

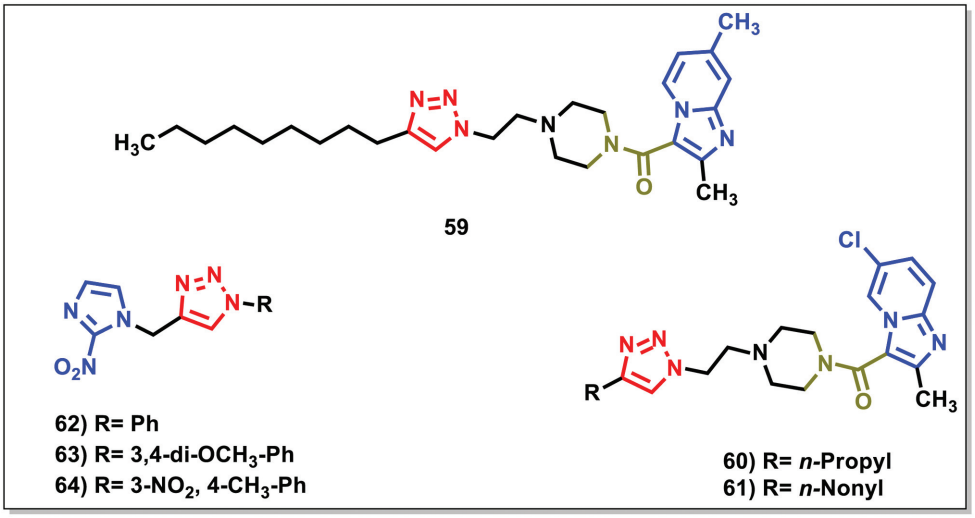
However, the three examined compounds **59**, **60,** and **61** (Fig. 20) with IC_{50} values of 5.5, 7.4, and 0.7 µM, respectively, showed substantial efficacy against the *T. brucei* parasite. The IC_{50} value for the subsequent compound **59** was only 10 times higher than that of the reference drug Melarsoprol (0.05 µM). Concerning the antitrypanosomal activity, SAR revealed that among all the examined series of compounds, those with bulky group/long-chain substitutions at the triazole nucleus **59** and **60** exhibited the strongest antitrypanosomal action [88]. In addition, different compounds bearing 1,2,3-triazole-nitroimidazole scaffold were synthesized by Elvis *et al.* using the click chemistry approach and evaluated as their antitrypanosomal activity. It was demonstrated that the promising potential candidates for future *in vivo* investigations against *Trypanosoma cruzi* are compounds **62**, **63,** and **64** (Fig. 20) [90]. Structure–activity relationship displayed that compound **62** without substituents on the phenyl ring had biological activity comparable to that of benznidazole (BZN), with good IC_{50} values of 3.1 µM and 64.5 SI. Compound **63** with an IC_{50} value of 0.65 µM was 5 times as active as benznidazole and displayed an extraordinary selectivity index (SI > 307.7). Compound **64** contains electron-donating groups in the fourth position and an electron-withdrawing substituent in the third position. This compound demonstrated 2.5 times the activity of BZN with an IC_{50} of 1.2 µM and an excellent SI >166.7. Therefore, it is conceivable to

Figure 19



Revealed interactions between the highly active compound **58** and the target protein's active site amino acids [88].

Figure 20



Different 1,2,3-triazole hybrids having antitrypanosomal activity.

believe that the 3-OCH_3 or 3-NO_2 groups, which are present in **63** and **64**, may establish hydrogen bonds with the therapeutic target present in the parasites, boosting their antitrypanosomal activity [90].

In the search for unique medications to treat leishmania, a group of eugenol derivatives bearing 1,2,3-triazole moiety had been synthesized through CUAAC and evaluated as an antileishmanial agent. Among all the evaluated derivatives, compared with pentamidine and glucantime, compound **65** (Fig. 21) had strong antileishmanial activity and a selectivity index value of 132.5 that was superior. The majority of its physicochemical and pharmacokinetic characteristics were likewise within the ranges expected for orally administered drugs. The findings imply that these substances can be used as exciting new prototypes for leishmaniasis medication development [91].

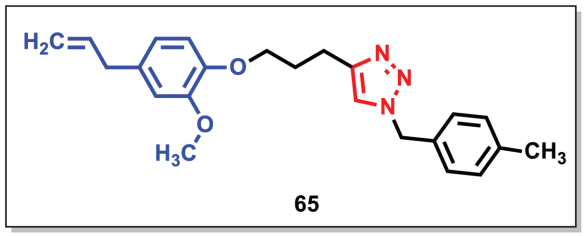
In another recent research, a series of 6-amidinobenzothiazole-1,2,3-triazole ring linked through phenoxymethylene were synthesized and evaluated *in vitro* against the protozoan parasite *Trypanosoma brucei*. Racane *et al.* demonstrated that benzothiazole imidazoline containing a phenoxymethylene linker, compound **66** (Fig. 22), with the p-chlorophenyl analog showed the most potent antitrypanosomal activity ((IC_{50}=0.09 µM and IC_{90}=0.12 µM) when compared with the standard drug Nifurtimox [89]. SAR revealed that phenoxymethylene linker increased the antitrypanosomal activity while replacement of the phenoxymethylene linker with a direct fusion of benzothiazole to1,2,3-triazole reduced antitrypanosomal activity against bloodstream forms of *T.brucei* .Also, imidazoline ring improved the activity of compound **66.**

Anti-inflammatory activity

Rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disorders, and psoriatic arthritis are all chronic diseases brought on by inflammation. The body's organs suffer further harm from inflammation, which is an important reaction to possible threats. The health and endurance of people are seriously threatened [92]. The social and economic burden is greatly affected globally. Nonsteroidal anti-inflammatory medicines have shown effective suppression of the enzymes glycosidase, AR, and SDH. NSAIDs like Ibuprofen and Indomethacin function by preventing the cyclooxygenase (COX) enzymes from catalyzing the prostaglandin production process using arachidonic acid. There are two isoforms of cyclooxygenase enzymes (COXs): the intrinsic form (COX-1) and the triggered form (COX-2) [93]. Zhang and coworkers designed and synthesized a group of compounds generated by combining 1,2,3-triazole moieties to ursolic acid in order to discover new anti-inflammatory drugs. The compounds generally showed strong anti-inflammatory activity when tested for their ability to reduce inflammation utilizing an ear edema model. Cyclooxygenase COX-1/COX-2 inhibition experiments were performed in vitro using the potent anti-inflammatory drug. The most active compound of all those made was compound **67** (Fig. 23), which showed 82.81% inhibition following intraperitoneal delivery, outperforming celecoxib as a positive control. The explanation for the interaction of compound **67** with COX-2 enzyme is revealed by molecular docking data (Fig. 24). Additional research showed that compound **67** had potent COX-2 inhibitory activity, with an IC_{50} value of 1.16 µM and a selectivity index (SI) value of 64.66, which was comparable to celecoxib (IC_{50}=0.93 µM, SI = 65.47) [93].

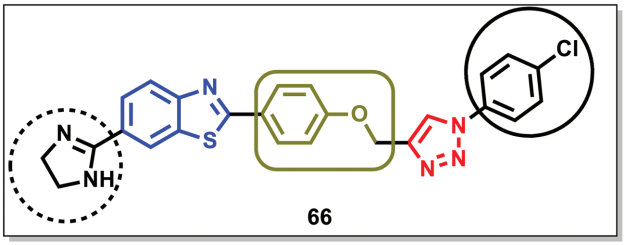
In addition, new coumarin-based 1,2,3-triazole derivatives had been designed and synthesized as anti-inflammatory agents. All of the synthetic compounds had their in vitro anti-inflammatory

Figure 21



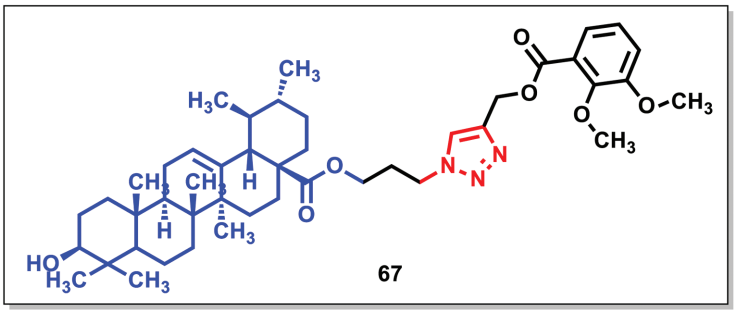
A derivative of eugenol with a 1,2,3-triazole moiety acting as an antileishmanial agent.

Figure 22



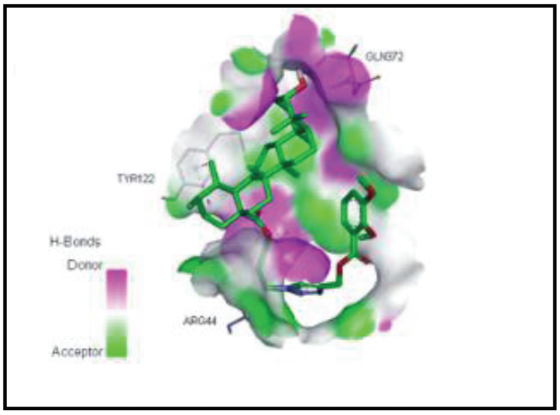
Benzothiazole linked to 1,2,3-triazole through the phenoxymethylene linker as an antitrypanosomal agent.

Figure 23



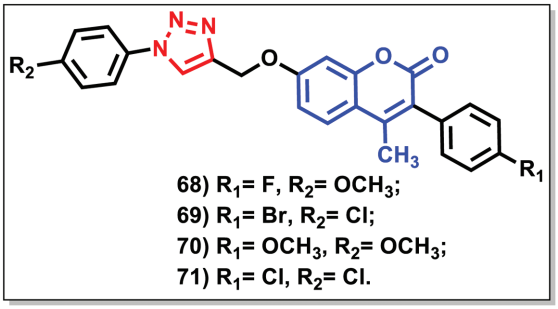
Ursolic acid derivative bearing 1,2,3â triazole moiety as an anti-inflammatory drug.

Figure 24



Docked framework for COX-2's active compound **67** [93].

Figure 25



New coumarin-based 1,2,3-triazole hybrids as anti-inflammatory agents.

activity tested using the heat-induced hemolytic method and the egg-albumin method, both of which used Diclofenac as the reference drug. Compound **68** (IC_{50}=15.78 µM/ml) performed significantly better than Diclofenac (IC_{50}=17.52 µM/ml) in the egg-albumin technique. Compounds **69**, **70**, and **71** showed excellent activity in the heat-induced hemolytic technique (IC_{50} values: 15.35 µM/ml, 15.90 µM/ml, and 17.11 µM/ml, respectively) (Fig. 25) [94].

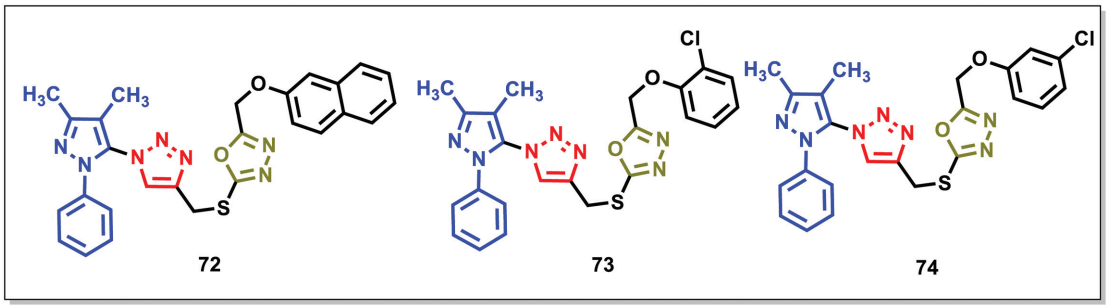
Also, Kumar *et al.* designed and synthesized a series of compounds bearing pyrazole, oxadiazole conjugated with 1,2,3-triazole moiety using the one-pot three-component azide–alkyne cycloaddition. Using a bovine serum albumin denaturation assay, the novel synthesized compounds were tested for in vitro anti-inflammatory efficacy. In comparison to the standard drug diclofenac sodium, compounds **72, 73,** and **74** (Fig. 26) demonstrated remarkable anti-inflammatory properties with IC_{50} values of 28.22, 27.90, and 24.33 µM/ ml, respectively. *In silico* binding interactions with COX-2 and the potency of **73** and **74** in the bovine serum albumin denaturation assay suggest that these compounds may make good anti-inflammatory drug candidates. The amino acid SER530A forms a hydrogen bond with the two compounds **73** and **74**, binding them to the active site of the enzyme with binding affinity values of –6.3 and –6.1 kcal/mol, respectively [95].

Miscellaneous activities

In recent years, various synthetic methods based on 1,2,3-triazole derivatives for the antimalarial activity have been established. Different derivatives with 1,2,3-triazole-tethered isatin-ferrocene conjugates and 4-aminoquinoline-ferrocenenylchalcone conjugates were created and synthesized. Compound **75** was the most potent and noncytotoxic conjugate, exhibiting an IC_{50} of 0.37 µM against the CQ-R W_2 strain, while compound **76** exhibited an IC_{50} of 3.76 µM against the 3D7 strain of *P. falciparum* [96,97]. It also exhibited β-amino alcohol grafted 1,2,3-triazole derivative **77** potent *in vitro* antiplasmodial activity as well as *in vivo* antimalarial activity [98].

Moreover, the imidazo[1,2-*a*]pyridines **78** and **79** produced promising antiepileptic effects [99].

Figure 26



1,2,3-triazole-tethered pyrazole and oxadiazole as new anti-inflammatory candidates.

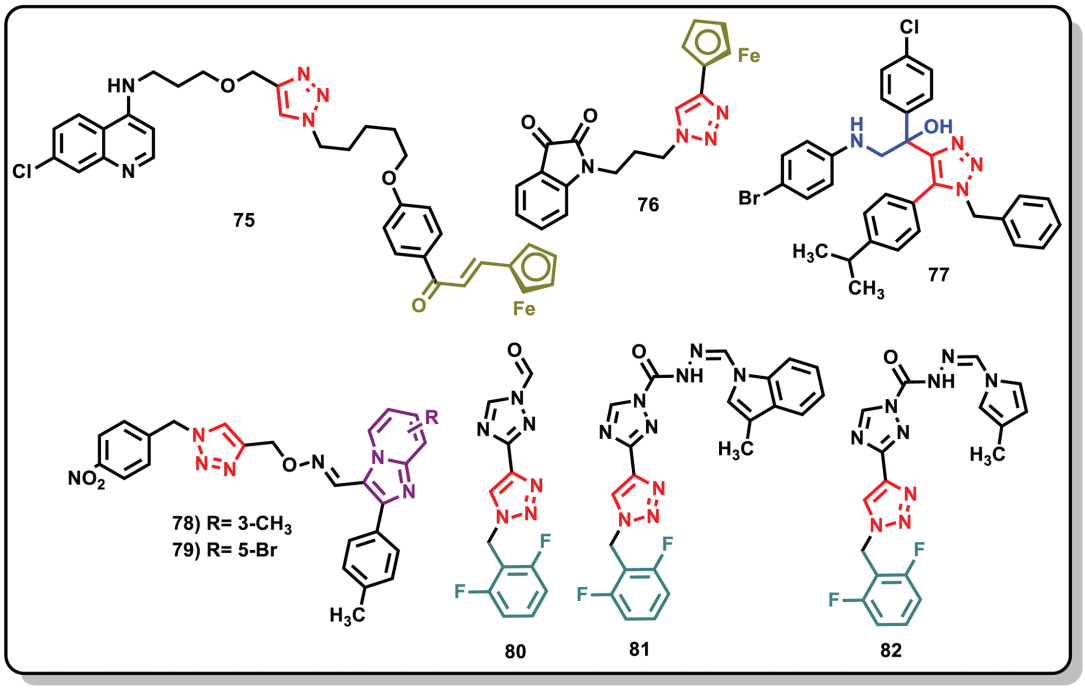
Similarly, 1-(2,6-difluorobenzyl)-1*H*-1,2,3,-triazole derivatives **80–82** showed a promising anticonvulsant profile.

In addition, a set of DNA aptamers that interact with thrombin have been developed, which contain internucleotide linkages of 1,2,3-triazole. The developed aptamers have a structural similarity to the widely recognized thrombin-inhibiting G-quadruplexes TBA15 and TBA31. The aptamers that were developed offer a promising substitute to the existing DNA-based anticoagulant agents. This is because the use of triazole internucleotide linkages has resulted in the aptamers having high acidity and resistance to nuclease digestion (Fig. 27). [100,101].

Conclusion and future perspectives

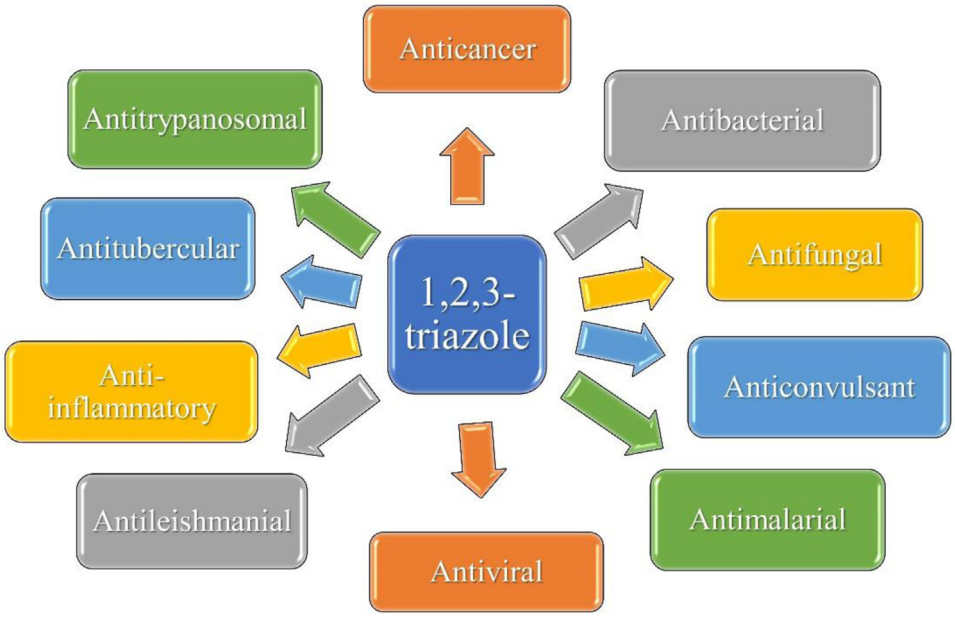
1,2,3-Triazole is a ring system that consists of five members, is aromatic and heterocyclic, and has three nitrogen atoms and a high electron density. The vast array of scaffolds provided by it has enabled successful research and development, leading to effective cures, low toxicity, and superior pharmacokinetic properties, which have greatly contributed to improving the treatment of human diseases. Many 1,2,3-triazole-based derivatives have been successful in moving from clinical trials to the later phases, and some have even reached the clinics. However, despite the fact that many 1,2,3-triazole compounds have failed to advance the therapeutic development pipeline, they nonetheless serve as intriguing starting points for

Figure 27



Different 1,2,3-triazole derivatives with miscellaneous activities.

Graphical abstract



future optimization or drug repurposing techniques. This study emphasizes the broad therapeutic relevance of different 1,2,3-triazole compounds in various therapeutic areas, including anticancer, antimicrobial, antitubercular, antileishmanial, antitrypanosomal, and anti-inflammatory diseases. This review also shows the adaptability of oxazolidinones in medicinal chemistry. To shed light on this significant chemical motif and to spark conversation about their current and potential uses in drug development, the objective of this study was to present a thorough overview of all oxazolidinone analogs that have been described in the literature over the previous 10 years.

Acknowledgements

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Nil.

Conflicts of interest

There are no conflicts to declare.

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