Chapter 11
An Overview on Biological Activities of 1,2,3-Triazole Derivatives

Arup K. Kabi, Sattu Sravani, Raghuram Gujjarappa, Aakriti Garg, Nagaraju Vodnala, Ujjawal Tyagi, Dhananjaya Kaldhi, Virender Singh, Sreya Gupta, and Chandi C. Malakar

Abbreviations

NSAID	Non-steroidal Anti-inflammatory Drugs
HIV	Human Immunodeficiency Virus
RSV	Respiratory Syncytial Virus
DNA	Deoxyribonucleic Acid
EGFR	Endothelial Growth Factor Receptor
COX	Cyclooxygenase
AA	Arachidonic Acid
U.S. FDA	United State Food and Drug Administration
ADP	Adenosine di-phosphate
LOX	Lipoxygenase
TNF-α	Tumour Necrosis Factor Alpha
RNA	Ribonucleic Acid
SAR	Structure–Activity Relationship
MTB	Mycobacterium Tuberculosis
DPPH	2,2-Diphenyl-1-picrylhydrazyl
TcTS	T. cruzi trans-sialidase
WHO	World Health Organization

A. K. Kabi · R. Gujjarappa · N. Vodnala · U. Tyagi · D. Kaldhi · C. C. Malakar (✉)
Department of Chemistry, National Institute of Technology Manipur, Imphal, Langol, Manipur 795004, India
e-mail: cmalakar@nitmanipur.ac.in

S. Sravani · A. Garg · S. Gupta (✉)
Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Chunilal Bhawan, 168, Maniktala Main Road, Kolkata 700054, India

V. Singh
Department of Chemistry, Department of Chemistry, Central University of Punjab, Bathinda, Punjab 151001, India

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HDAC	Histone Deacetylases
COVID-19	Coronavirus Disease-2019
MDCK	Madin Darby Canine Kidney
EBV	Epstein-Barr Virus
UV	Ultraviolet

1 Introduction

1,2,3-Triazoles and their derivatives are among the topmost immense *N*-heterocyclic scaffolds because of the widespread spectrum of pharmacological and biological activities [1–4]. Triazoles are the five-membered heterocycles embedded with three consecutive nitrogen-atoms that can be synthesised simply utilizing 'click' chemistry through ruthenium- or copper-catalysis between azides and terminal alkynes by cycloaddition reactions [5]. However, the 'linker' feature of 1,2,3-triazoles was established and distinct 1,2,3-triazole-based conjugates and hybrids were prepared and appraised as prime compounds for various biological and pharmacological targets due to their specificity, reliability and biocompatibility [6].

Furthermore, 1,2,3-triazole-based scaffolds have several convenient attributes such as immense chemical reliability (generally inactive to basic or acidic hydrolysis and reducing and oxidizing reactions even at higher temperature), effective dipole moment (4.8–5.6 Debye), capability of hydrogen bonding and aromatic character, which enhances their aptitude and solubility to interact with biomolecular targets as well as highly stable to metabolic degradation [7]. 1,2,3-triazole and its derivatives exhibit numerous biological activities such as anti-proliferative, anti-HIV, anti-inflammation, antimicrobial, anticonvulsant, anti-leishmanial, anti-trypanosomal, etc. [8–15]. Moreover, these motifs are usually steady for hydrolysis in both acidic and basic conditions along with oxido-reductive environment, making them steady to metabolic deterioration and designates upraised aromatic compensation. Furthermore, these enormous properties reveal the functionalised 1,2,3-triazoles skeletally appearing the amide bond and capable toward mimicking an *E* or a *Z* amide bond. Several well-known pharmacophore that possesses 1,2,3-triazole motif are existing in the market as an anticancer medication carboxyamidotriazole, wide spectrum cephalosporin antibiotic cefatrizine, β-lactam antibiotic tazobactam and anticonvulsant drug Rufinamide, etc. [5]. In this chapter, modern advancements in the improvement of 1,2,3-triazole-based pharmacologically active molecules are highlighted (Fig. 1).

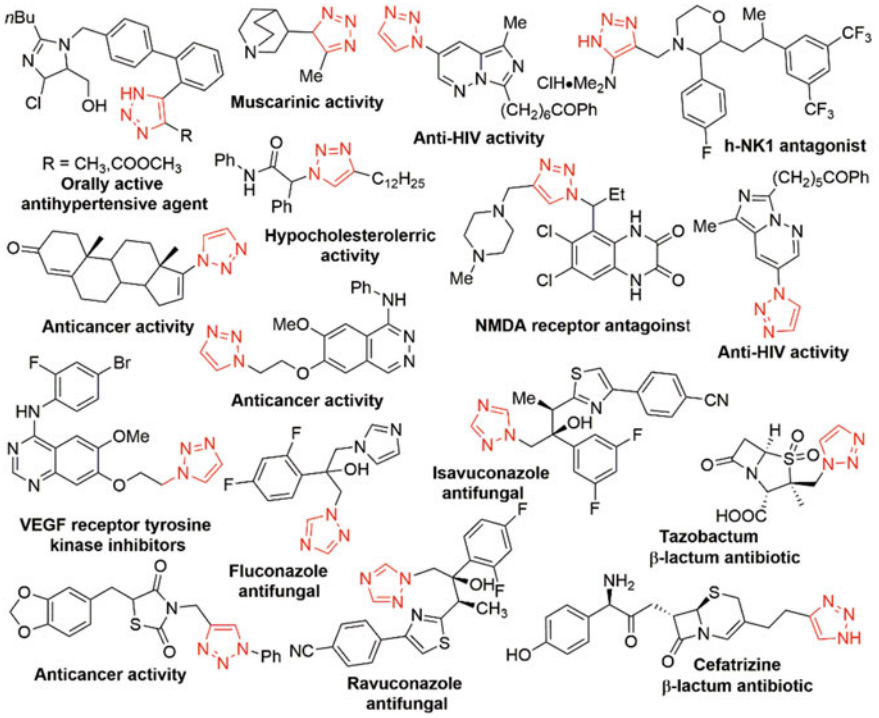


Fig. 1 Triazole embedded bioactive and drug molecules [1–6]

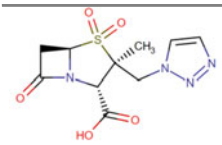
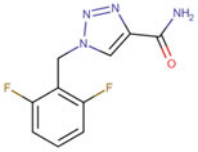
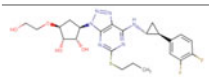
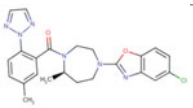
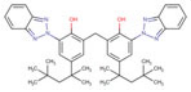
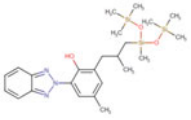
1,2,3-triazoles are the bioisosteres of amide bonds because of their electronic and structural resemblance and possess higher stability towards metabolic degradation. The pharmacological activities exhibited by 1,2,3-triazoles are anticancer, antimicrobial, anti-HIV, antimalarial, anti-inflammatory, antifungal, antiallergic, antiepileptic, anti-leishmanial, antituberculosis and anthelmintic activities [16]. They are proficient in forming hydrogen bonding interaction, enhancing their solubility and capacity to combine with biomolecular targets [17].

Few of the FDA approved 1,2,3-triazole containing drugs are listed in Table 1 [2].

2 Anticancer Activity of 1,2,3-Triazole Derivatives

Cancer is the principal health threat around the globe and affects a wide majority of the global community. In this contrast, several anticancer agents conveyed for medication of diverse types of cancers act through distinct mechanisms [18]. Nevertheless, the main side effect related to these anticancer agents is cytotoxicity towards the healthy cells because of inadequacy in specificity for the abnormal cells. 1,2,3-Triazoles have been investigated for the last 30 years as well as inspected mostly for

Table 1 FDA approved 1,2,3-triazole containing drugs [2]

Structure of the drug Name of the drug (drug bank ID)	Category/indication	Mechanism of action
 Tazobactam (DB01606)	Used amalgamation with ceftolozane or piperacillin to increase the antibiotic spectrum of piperacillin	Irreversible inhibitory effect on beta-lactamase enzymes
 Rufinamide (DB06201)	Additive therapy for the medication of seizures correlated with Lennox-Gastaut syndrome	Extends the inactive state of voltage-gated sodium channels accordingly stabilising membranes
 Ticagrelor (DB08816)	For the preclusion of thrombotic events such as heart attack or stroke in patients with myocardial infarction with ST elevation or Acute Coronary syndrome (ACS)	Reversible allosteric antagonist of P2Y12
 Suvorexant (DB09034)	For the treatment of insomnia	Dual antagonist of orexin receptors OX1R and OX2R
 Bisoctrizole (DB11262)	Designated as a sunscreen agent in cosmetic production	An organic ultraviolet A (UVA) strainer which consumes both UVA and UVB radiation
 Drometrizole trisiloxane (DB11585)	An active component in several sunscreens for the indication of protection of skin	Absorbing the harmful UV radiation of sunlight

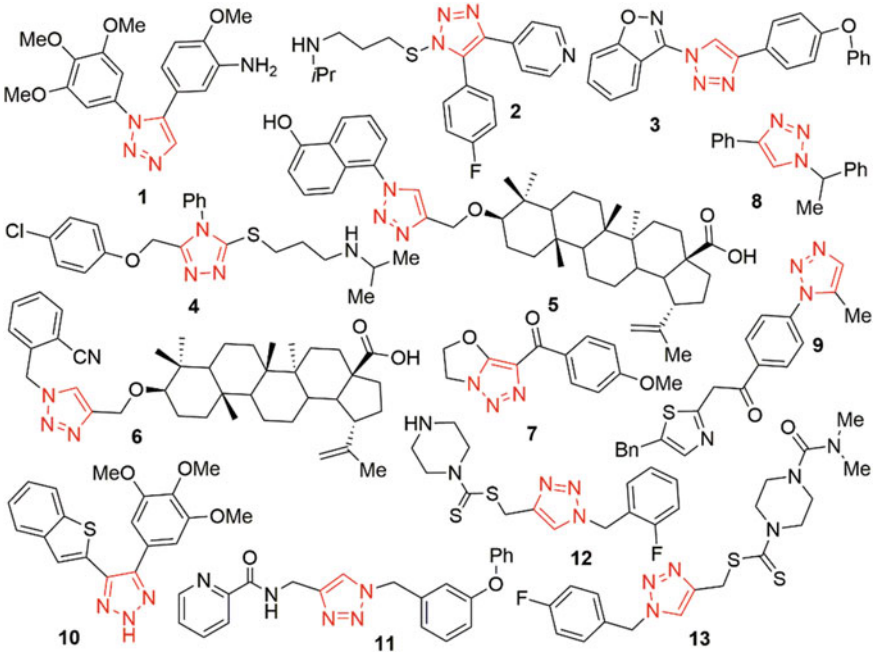


Fig. 2 Anticancer activity of 1,2,3-triazoles scaffolds [19–29]

the chemotherapeutic potential. However, numerous scientists and researchers all over the world have accomplished intensive exploration in this specific field. In this portion, we highlight modern advancements in the progress of 1,2,3-triazole-based pharmacologically active antineoplastic compounds (Fig. 2) [19–22].

Interestingly, the heterocyclic triazole such as 2-methoxy-5-(1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3- triazol-5-yl)aniline **1**, repressed tubulin polymerization. In addition, to explore the mechanism of cell death, DNA fractionation methodology was enrolled which exposed that the triazole-based compounds **2** and **4** encouraged DNA impair via apoptosis due to the biochemical ambience for these moieties and exceptional cytotoxic activity [23]. Additionally, 3-(4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzo [*d*]isoxazole (PTB) (compound **3**) was establish as atop most efficient antineoplastic agent against MV4-11 cells [24]. In addition, 4-[phenyl-1-(1-phenyl–ethyl)]-1*H*-1,2,3-triazole analogue **8** exhibited decent cytotoxicity counter to HL 60 cells. In continuation, two triazole-based compound, **3**{1 *N*(2-cyanophenyl)-1*H*- 1,2,3-triazol-4yl}methyloxy betulinic acid **6** and **7**{1 *N*(5- hydroxy-naphth-1-yl)-1*H*-1,2,3-triazol-4yl}methyloxy betulinic acid **5** showed remarkable anticancer activity against leukaemia cell line HL-60 [25]. In addition, compound, **7** displayed as the most effective derivative against K562 and A431 human tumour cell lines [26]. In continuation, compound **9** was found vastly effective to the leukaemia K-562 cell line and SK-MEL-5, which is one of a series of melanoma cell lines [27]. Additionally, compound **10** showed huge

potential in counter to Hs578T triple-negative breast cancer cell lines (TNBC) as well as showed the most powerful inhibition against tubulin polymerization [28]. In continuation, a series of *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)acrylamide (compound **11**), which encouraged M-phase (mitosis) arrest in immortal HeLa cells. Remarkably, among the series of 1,2,3-triazole-dithiocarbamate-urea hybrids, scaffolds **12** and **13** exhibited a wide range of anticancer activity against MGC-803 cells [29].

Quinazoline-4(3*H*)-one linked to 1,2,3-triazoles were assessed in contrast to various malignant cell lines; namely, three are human breast cancer cell lines (MDA-MB-231, MCF-7, T-47D), human lung carcinoma (A549) and prostate cancer cell lines (PC3). Three compounds have exhibited a potent anticancer activity compared to the reference drug, Etoposide in the cell line MDA-MB-231 with the IC_{50} values of 12.05 μM, 15.62 μM and 13.47 μM respectively whereas Etoposide IC_{50} values are 23.56 μM. Two compounds showed potency against A549, non-small cell lung cancer (NSCLC), in comparison to erlotinib. Docking study clearly indicates that 1,2,3-Triazole moiety executes a vital responsibility in suppressing activities of EGFR active site [30].

ErbB is a transmembrane glycoprotein with a molecular weight 170 KDa to 185 KDa. It consists of ErbB1/EGFR/HER1; ErbB2/HER2 Neu; ErbB3/HER3 and ErbB4/HER4. Quinazoline-4(3*H*)-one related to 1,2,3-triazoles inhibits the Endothelial growth factor receptor (EGFR). It is composed of three fragments: (a) extracellular *N*-terminal, (b) transmembrane domain and (c) intracellular tyrosine kinase. The extracellular *N*-terminal comprises four domains- I, II, III and IV. It binds to several ligands but the intracellular tyrosine kinase is highly preserved [31]. with the presence of Leucine, the domain I and III of extracellular *N*-terminal are rich whereas, in the presence of Cysteine, the domains II and IV are extremely observed [32].

EGFR (Endothelial growth factor receptor) can be found in two states, i.e. the Open state which is active and closed state which is inactive. Until a ligand is bound, both these states exist in equilibrium and it stabilises the open state, once the ligand is bound. For the Closed state; The domains II and IV have interaction in between them, existing on the extracellular *N*-terminal; however, any interaction with the ligand is not shown by the domains I and III. In open state, the domains I and III interact with the ligand when the domains II and IV move away (Fig. 3) [31].

In homodimerization and heterodimerization of the receptors on the extracellular N-terminal of EGFR, domain II is involved. The formation of dimer is asymmetric as well as characteristic, the small N-lobe of the one kinase binds with the large C-lobe of the other kinase domain. The activation of CDKs (cyclin-dependent kinases) and Src family kinases leads to this dimer formation [32].

All the series of the compounds occupied the active site of EGFR. The hook shape conformation in the binding model of inhibitors is because of the existence of triazole rings. The 1,2,3-triazole ring interacts with the amino acids present in the active site of EGFR receptors involves various interactions like electrostatic interaction, Pi-anion interaction, H-bonding and Van der waals interaction [30].

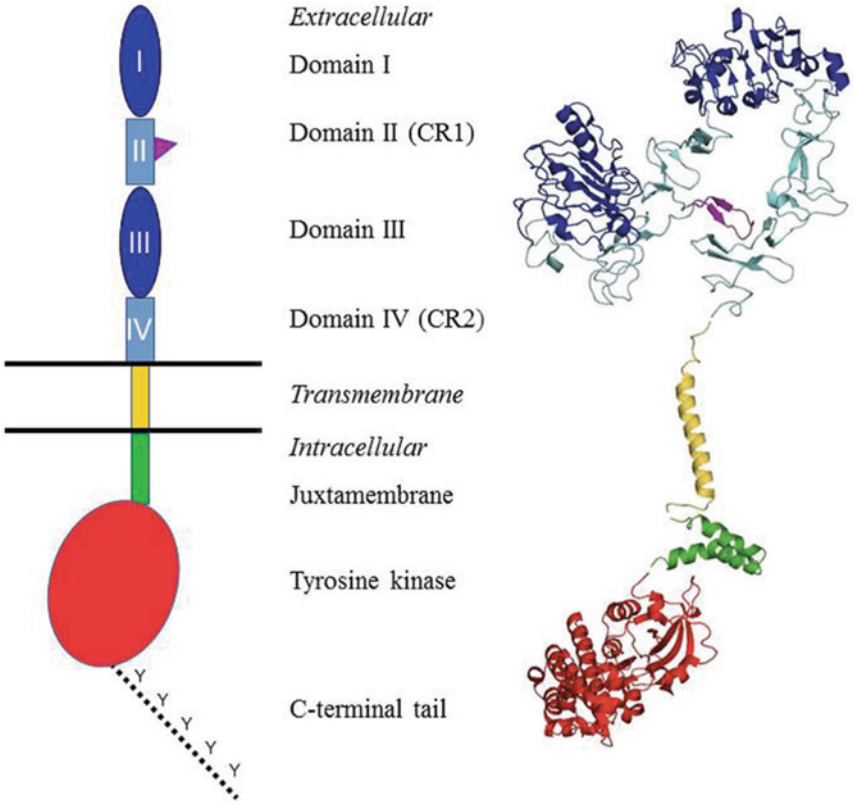


Fig. 3 Structural representation of EGFR [31]

Novel bis alkynes with di-substituted triazoles were synthesised and they were evaluated for the anticancer activities and identified that the bis alkynes themselves have some anticancer activity. In order to increase their anti-proliferative activity, many substitutions were done on the bis alkyne. The introduction of one triazole moiety in the bis alkyne has shown the deleterious effect on its anti-proliferative activity but introduction of one more triazole moiety makes it a good anticancer exhibiting compound. One of the bis triazole moiety is highly potent which exhibits the anti-proliferative activity in nanomolar range [33].

3 Anti-inflammatory Activity of 1,2,3-Triazole Derivatives

Amongst all biological processes, inflammation is the most important part of the immune system's response to infection and injury. It Comprises The release of arachidonic acid (AA) from phospholipids (are main components of the plasma membrane),

sustaining additional bioprocessing through 5-lipoxygenase (5-LOX) and cyclooxygenase (COX) pathways. Previously we have discussed the activity of many NSAIDs (non-steroidal anti-inflammatory drugs) such as ibuprofen, indomethacin and naproxen, which suppress arachidonic acid (AA) metabolism via inhibition of cyclooxygenase (COX). In this section of the chapter, modern advancements in the development of triazole-based pharmacologically active anti-inflammatory compounds are listed (Fig. 4).

In addition, to evaluate the anti-inflammation and antineoplastic action against various cancer cell lines, 1,2,3-triazole-embedded *N*-alkyl nitrone derivatives and *N*-phenyl nitrone derivatives were investigated. However, the measure of anti-inflammatory activity compounds **14** and **15** showed noteworthy inhibitory effect on Interleukin-1β (IL-1β) secretion [34]. In addition, compound **16** improved TNFα-enhanced cyclooxygenase-2 expression by Western blot analysis and showed to be extremely good on the molecular level, related to diclofenac, the standard drug [35]. In continuation, the compound **17** displayed good inhibitory effect on Glycogen Synthase Kinase-3β (GSK-3β) and also effective to prevent the inflammatory cytokines TNF-α (Tumour Necrosis Factor-α), IL-1β and Interleukin-6 (IL-6) extensively, related to standard anti-inflammatory drug, indomethacin, as well as a GSK-3β inhibitor, SB216763 [36]. Furthermore, compounds **18**, **19** and **20** show substantial inhibitory activity on Interleukin-1β (IL-1β) secretion, a scope of anti-inflammatory action [34]. In addition, greater specificity towards the cyclooxygenase

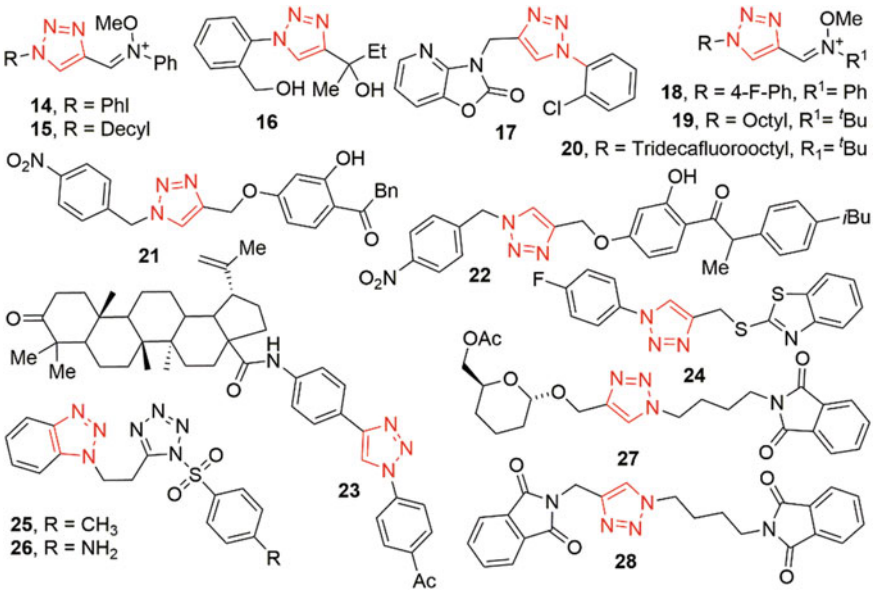


Fig. 4 Anti-inflammatory activity of 1,2,3-triazoles scaffolds [34–42]

-2 (COX-2) binding site were showed by a series of 1-{4-[(1H-1,2,3- triazol-4-yl)methoxy]-2-hydroxyphenyl}-2-phenylethanone derivatives **21**, an efficient anti-inflammatory compound [37]. In continuation, the protein–ligand relations between COX-2 (PDB code 4PH9) and desired compounds were availed for docking investigations and compound **22** anticipated the extremely good binding attitude to the active site of 4PH9 protein [38]. Additionally, a noteworthy anti-inflammatory activity showcased by betulonic conjugate **23**, suggested at the highest dose in comparison to the reference drug indomethacin. However, from the SAR study, upon altering of hexyl substitution at the triazole scaffolds onto a benzyl moiety and to a higher extent such as methoxyphenyl and acetyl phenyl substitution, revealed the possibility of enhancing the anti-inflammatory activity in triazoles [39]. In addition, compound **24** established good potential for the selective cyclooxygenase-2 (COX-2) inhibitory strain with COX-2/COX-1, however, the compound controlled major anti-inflammatory action is associated with the reference drug ibuprofen [40]. In continuation, 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzo[*d*][1,2,3]triazoles were anticipated to the effective anti-inflammatory as well as anti-nociceptive activities. The related compounds **25** and **26** produced greater anti-inflammation compared to reference drugs [41]. However, new 1,2,3-triazole-based phthalimide analogues were investigated for anti-inflammatory activities and the compounds **27** and **28** exhibited best activity [42].

Ibuprofen, an NSAID containing free carboxylic group, is responsible for some side effects like inhibition of Prostaglandin synthesis in GIT. So, modifications were done to the carboxyl group of the Ibuprofen. One of the modifications is the introduction of the five-membered heterocycle, 1,2,3-triazole. These novel triazole-containing compounds were synthesised and their anti-inflammatory movement was evaluated.

The anti-inflammatory actions of these molecules were monitored at the dose of 10 mg/kg body weight by a suitable method; namely, carrageenan-induced rat paw edema model and their obtained outcomes are correlated with the standard drug, Ibuprofen. One of these compounds has exhibited potential actions 94.01% after 3 h, 96.35% after 4 h, 95.62% after 5 h and 94.17% after 6 h when compared with the standard drug in 3 h 93.16%, in 4 h 95.62%, in 5 h 95.62% and in 6 h 94.70%. The other molecules have exhibited comparable to moderate anti-inflammatory activity. The side effects of the Ibuprofen compounds were reduced [38].

The 4,5-Dihydro-1*H*-1,2,3-triazoles were prepared and their activity was evaluated against standard drug, Ibuprofen. The anti-inflammatory activity was observed at various hours and the percentage inhibition was calculated. Two compounds have exhibited good anti-inflammatory activity with the % inhibition of 63.28% at 1 h and 67.12% at 3 h; 63.43% at 1 h and 68.07% at 3 h respectively and the Ibuprofen activity was 64.06% at 1 h and 68.10% at 3 h [43].

4 Anti-tubercular Activity of 1,2,3-Triazole Derivatives

Over the last few decades, there has been considerable growth in occurrences of tuberculosis specifically, via drug-resistant *Mycobacterium tuberculosis* (M. tb), a species of pathogenic bacteria. Anti-tubercular medications such as rifampicin, pyrazinamide, isoniazid, streptomycin and ethambutol (known as antibiotics) are very often inadequate. Hence, there is a need for developing more advanced anti-tubercular compounds, in this context, here we are providing few active compounds against tuberculosis (Fig. 5) [44–54].

In exploration of novel potent molecules in contrast to *M. bovis BCG* and *M. tuberculosis* (MTB) H37Ra, interestingly 1,2,3-triazoles-based benzothiazinone (compounds **29** and **34**) were exhibit maximum potential against *M. bovis* BCG and MTB [44]. In addition, for the inhibition of H37Rv strain, an approach was bashed by employing 1,2,3-triazoles including fluorine-embedded benzimidazole series. Additionally, these compounds were potentially valuable for the anti-tubercular activity and mostly the compounds **30**, **31** and **32** displayed better activity associated with standard rifampicin [45]. In continuation, compound **33** exhibited two-fold greater competence than the reference drug econazole, signifying that the scaffold is expected to be improved for the anti-tubercular activity [46]. Furthermore, *N*-substituted-phenyl-1,2,3,-triazole-4-carbaldehydes were screened and the compounds **35** and **36** exhibited the best inhibition [47]. In continuation, 1,2,3-triazole conjugates of 2-mercaptobenzothiazole were considered and screened to the *M. tuberculosis* H37Rv strain for anti-tubercular activity. The related compounds **37**, **38** and **39** inhibited the growth of *M. tuberculosis* H37Rv strain [48]. In addition, compound **40** was exposed as an effective compound counter to *M. tuberculosis* (MTB) [49]. Furthermore, compound **41**, i.e. 1-dodecyl-4-phenethyl-1*H*-1,2,3-triazole exhibited inhibition against *M. tuberculosis* H37Rv [50]. Additionally, compound **42** showed a

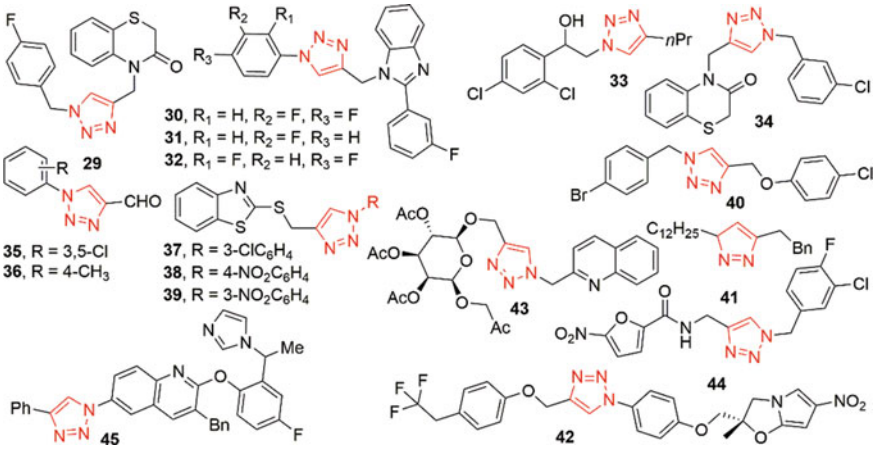


Fig. 5 1,2,3-triazoles moieties with anti-tubercular activity [44–54]

harmonious activity in combining studies with no CYP-inhibition and first line-TB drugs [51]. In continuation, quinoline-derived triazole sugar hybrid, **43** showcased potential as an effective compound in contrast to *M. tuberculosis* H37Rv strain through LRP (Luciferase Reporter Phage) assay [52]. Additionally, 5-nitrofuran–triazole conjugates screened for antibacterial as well as anti-tubercular action. In continuation, amidst all the tested scaffolds, **44** exhibited auspicious bioactivities against tuberculosis [53]. However, compound **45** inhibited *M. tuberculosis* H37Rv. The SAR was proposed that electrostatic interactions and hydrogen bonding interaction of polar functional groups of anti-mycobacterial compounds and amino acids of ATP-synthase of bacteria, which might be the plausible incentive for the potent activity [54].

Some 1,2,3-triazoles were prepared and these molecules were evaluated for anti-tubercular action in contrast to a virulent strain of MTB (MTB H37Ra; ATCC 25,177). The parameter taken into consideration was inhibition of growth of the virulent strain. Many compounds have exhibited the activity against MTB with the MIC range of 5.8–29.9 μg mL-1. These compounds showed movement with the IC_{50} of 0.2 μg/mL to 8.3 μg/mL. But these compounds have not exhibited the comparable activity with Rifampicin. Antioxidant activity is important for anti-tubercular drugs because of oxidative stress, which can lead to chronic inflammation. So, the antioxidant properties for these compounds were evaluated by employing 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. Five compounds have exhibited excellent antioxidant activity when compared to BHT and vitamin C (ascorbic acid) with the IC_{50} values of 10.1 μg/mL, 10.9 μg/mL, 12.1 μg/mL, 11.0 μg/mL and 11.4 μg/mL whereas the IC_{50} values of the standard drugs were 16.5 μg/mL and 12.7 μg/mL respectively.

The reported mechanism of 1,2,3-triazole derivatives showed inhibition to the DprE1 (decaprenylphosphoryl-β-D-ribose-2′-epimerase) enzyme of MTB and it is involved in the biosynthetic pathway of an important component of mycobacterial cell wall, i.e. decaprenyl phosphoryl-D-arabinose (DPA). These compounds were docked with the enzyme DprE1. The docking studies have revealed that the triazole ring exhibits various interactions by virtue of the amino acid residues present in the active site of DprE1 through hydrophobic bonds and Vander Waals interactions and they have shown the binding energy of −77.97 kcal/mol, −73.79 kcal/mol and −66.58 kcal/mol. The compounds with the triazole ring exert a good anti-tubercular activity [55].

5 Anti-leishmanial and Anti-trypanosomal Activity of 1,2,3-Triazole Derivatives

Trypanosomatids are protist protozoan parasites that affect millions of people all over the world and cause many significant human and animal diseases. Leishmania which is a genus of trypanosomes, thus blameworthy for leishmaniasis diseases. According

to WHO, more than 0.9–1.6 million new cases arise every year and 21 species are well-known sources for disease in people. In several countries, kinetoplastids, a ubiquitous group of flagellated protozoa, cause trypanosoma cruzi (chagas' disease), Leishmania species (leishmaniasis) and African trypanosomes (African sleeping sickness). These tropical diseases are specifically injurious in susceptible populations, predominantly amidst immunocompromised people or children which forcefully diminish human potential, moreover keeping people in poverty [56–68].

In briefly, 1,4-diaryl-1,2,3-triazole scaffolds were investigated in contrast to *Leishmania amazonensis promastigotes* and the analogues **46** and **51** exhibited extreme potency counter to Leishmania amazonensis (*L. amazonensis*) and Leishmania infantum (*L. infantum*) [56]. Additionally, triazolopyridopyrimidines **47** and **48** were discovered as more effective and screened against *L. infantum amastigotes*, related to the reference drug miltefosine [57]. In continuation, compounds **49** and **50**, related to the alkyltriazoles, exhibited dynamic activity counter to promastigote and amastigote forms in comparison with standard pentamidine and amphotericin B [58]. In addition, the 4-(3-nitrobenzyl)-1,2,3-triazole 5'-substituted guanosine analogue **52** displayed extreme potential on axenic amastigotes [59]. Furthermore, 1,2,3- triazole-derived *O*-benzylquercetin glycoconjugates were screened for anti-leishmanial action and among all the investigated analogues, **53** exhibited potent effectiveness related to leishmaniasis [60]. In continuation, *N*-[(1-benzyl-1*H*-1,2,3-triazole-4-yl)methyl] moiety, functionality on the C-2 amine of thiadiazole screened for anti-leishmanial action counter to the standard promastigote and 4-methylbenzyl analogue **54** was found to be the most effective compound against promastigotes [61]. Additionally, 1,2,3-triazolylsterols were screened against *L. donovani* and compound **55** was found to be potent against *Leishmania donovani* (*L. donovani*) and showed 5-times potent than the reference drugs [62]. Furthermore, it was established that diamidines **56** showed good potential against anti-trypanosomal activity than the standard melarsoprol, curing all infected mice [63]. Additionally, difluoromethylene 1,2,3-azole derivative **57** exhibited inhibition against the parasite growth expressively [64]. In addition, compound **58** contrary to the anti-parasite infections; exhibited promising effects [65]. In continuation, 5'-aryl-5'-deoxyguanosine analogues screened against *L. donovani* and compound **59** was found to be the most effective in the series without cytotoxicity [66]. In addition, 1,2,3-triazoles-linked 1,4-naphthoquinones based on nor-α-lapachone and nor-β-lapachone, moreover among the screened naphthoquinone analogues, nor-α-lapachone derivatives (compounds **60** and **61**) exhibited the highest anti-leishmanial activity [67]. However, sialic acid-6-O-galactose coupled to 1,2,3-triazole and the sialic acid galactopyranoside analogue **62** exhibited potential effect on *Trypanosoma cruzi trans-sialidase* (TcTS) inhibition (Fig. 6) [68].

However, the new analogues of long-chain alkyl [1,2,3-triazoles] and two alkylphosphocholine derivatives comprising azide scaffold and some peptide-based triazoles were screened for the inhibition of cysteine protease rCPB2.8. rCPB2.8 is one of the targets for anti-leishmanial drugs [69].

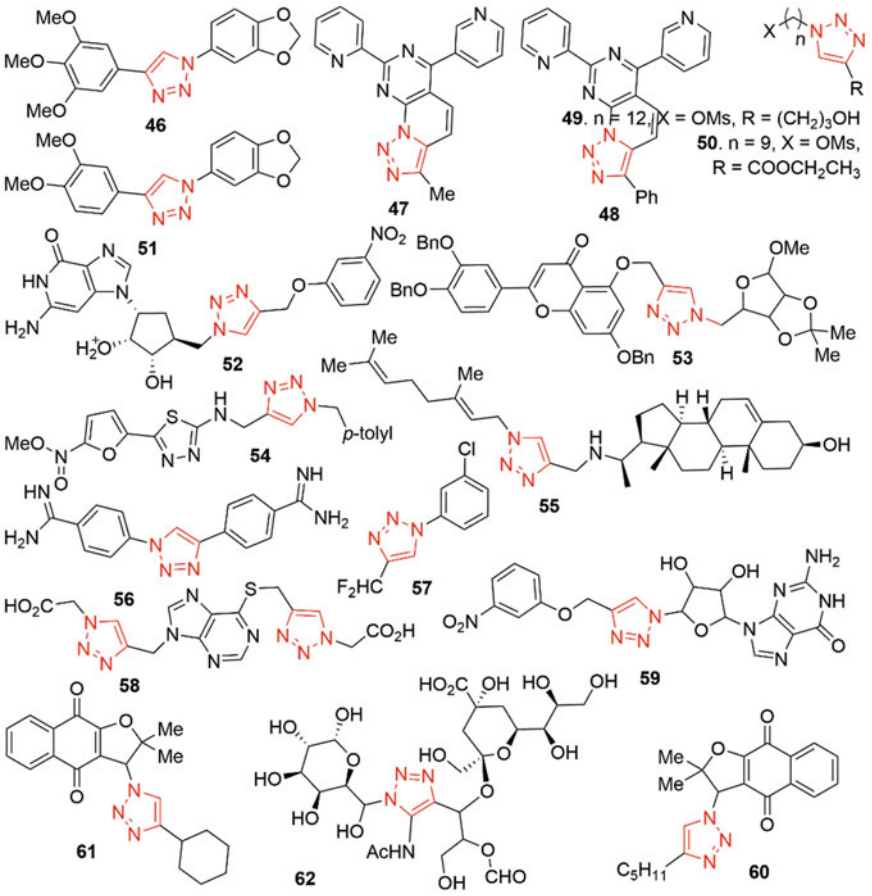


Fig. 6 1,2,3-triazoles moieties with anti-leishmanial and anti-trypanosomal activity [56–68]

Oyelere et al. reported that aryltriazolylhydroxamates with 1,2,3-triazole as a surface-recognition cap-group-linking and spacer-group chain lengths exhibited their potency as histone deacetylase (HDAC) inhibitors. Nevertheless, the addition of 1,2,3-triazole enhanced anti-leishmanial as well as antimalarial activities [70].

6 Antimicrobial Activity of 1,2,3-Triazole Derivatives

Antimicrobial resistance (AMR) is one of the top 10 worldwide public health emergencies, in agreement with the World Health Organization (WHO). It causes more than 23,000 deaths and 2 million infections per year [71]. It has been reported

globally, the struggle of pathogenic bacteria (which are capable of causing infections when entering into the body through water, air or physically) regarding available drugs. Furthermore, because of imperceptive antifungal activities, the occurrence of fungal infections improved swiftly as well as increased resistance. Therefore, scientists and researchers have mainly been focused on the improvement of novel antimicrobial agents for bacterial infections [72]. In this regard, diverse 1,2,3-triazole-based analogues display auspicious antimicrobial activities. However, molecules containing 1,2,3-triazole ring systems as novel antimicrobial agents has been described in this section [73–91].

The recently prepared scaffolds were investigated toward the antibacterial efficacies against gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Shigella boydii*as well as gram-positive bacteria like *Staphylococcus aureus*, *Enterococcus faecalis* and showed antifungal action in contrast to pathogenic yeast such as *Candida albicans*, *C. tropicalis*, *C. Parapsilosis*, *Cryptococcus neoformans*, *Dermatophyte* as well as Aspergillus, the moulds (a type of fungus) like *Aspergillus niger*, *A. fumigates*. Among these investigated compounds, compound **63** exhibited auspicious antifungal activity as well as potent antibacterial action [74]. In addition, spirocyclic triazolyl derivatives keep noteworthy biological activities and compound **64** screened against six diverse microbial strains and showed decent antimicrobial activity [75]. In continuation, compounds **65** and **66** were exhibited antibacterial and antifungal activity and this is mostly because of existence of halo-substituted phenyl rings and a piperazine ring in the frame [76]. Additionally, triazole-based moieties, i.e. compound **67** and **68** displayed important minimum inhibitory concentrations (MIC) and exhibited dynamic potential against several gram-positive and gram-negative bacteria like *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa* [77]. Indeed, compounds **69** and **70** exhibited enhanced antibacterial activity [78]. In addition, compound **71** exhibited more potency than the standard ampicillin counter to gram-positive (*Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli*) and exhibited considerable cytotoxicity and antifungal activities [79]. In continuation, 3,4-dichlorobenzyl analogue **72** and consistent hydrochloride **74** exposed potent activity against anti-*E. coli* compared to reference drugs Norfloxacin and Chloromycin. In addition, it was proved by initial data that, compound **72** could efficiently interpolate into calf thymus DNA to form 828-DNA conjugate by blocking DNA replication and establishing antimicrobial actions [80]. Indeed, compound **73** evaluated towards anti-bio-film, antimicrobial and bactericidal actions and showcase maximum potency and as well as promising cytotoxicity (Fig. 7) [81].

In addition, compounds **75** and **76** seemed more auspicious antibacterial agents against gram-positive bacteria (*S. aureus*, *S. epidermidis* and *B. subtilis*) as well as gram-negative bacteria (*E. coli*, *P. aeruginosa*, *S. typhi* and *K. pneumoniae*) [82]. Further, coumarin-based triazole derivatives (compound **77**) exhibited comparable antifungal activity in comparison with reference drugs [83]. In addition, compounds **78** and **79** displayed decent potency in contrast to bacteria and fungi [84]. In continuation, compound **80** (with 4-pentylphenyl substituent), showed durable inhibitory

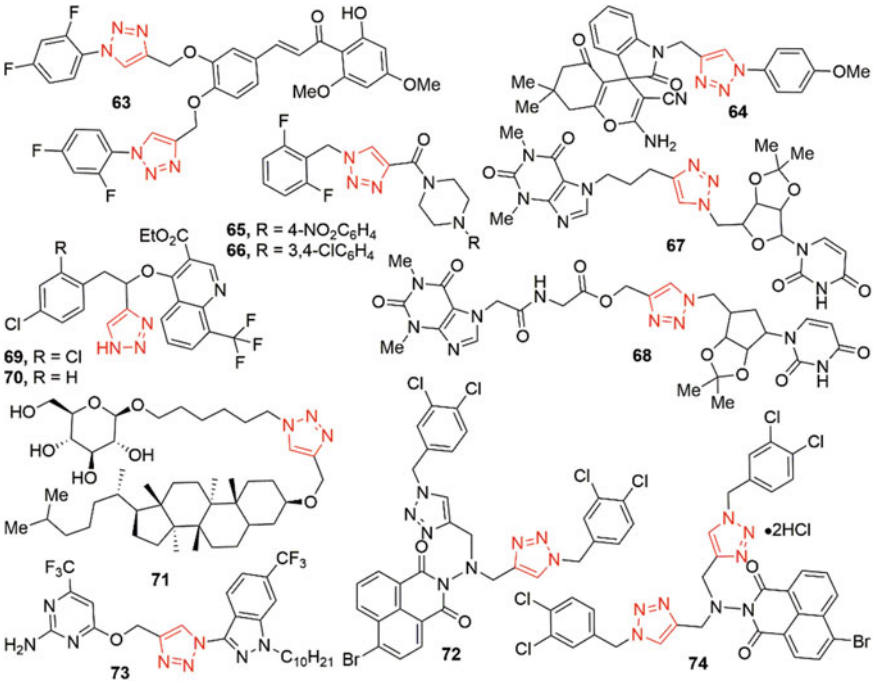


Fig. 7 Antimicrobial activity of 1,2,3-triazoles-based compounds [73–81]

action counter to bacteria and **85** (with 4- bromophenyl substituent) has a greater antifungal potency. Additionally, the above-mentioned analogues displayed a decent cytotoxic activity against a number of verified tumour cell lines, nevertheless non-toxic to the non-tumour liver cells [85]. Indeed, compound **81** exhibited outstanding antibacterial strain related to the standard drug Vancomycin, whereas **88** displayed better potency contrary to yeast [86].

In continuation, compounds **82** and **87** resulted in a stimulating antimicrobial strain in contrast to the screened bacteria and fungi omitting *E. coli*, which displayed slight counter action [87]. In addition, compounds **90** and **89** were exhibited effective antibacterial and antifungal strain respectively [88]. Indeed, compound **90** drew two-fold more antifungal activity than the standard miconazole, as well as extremely potent to diverse bacterial strains [89]. In addition, compound **86** showcased an extremely good discriminatory toxicity contrary to microorganisms [90]. However, 1,2,3-triazole attached carboxylic acid, bromoquinoline analogues were investigated and among all compounds, **89** displayed effective potential to antimicrobial and antifungal strains (Fig. 8) [91].

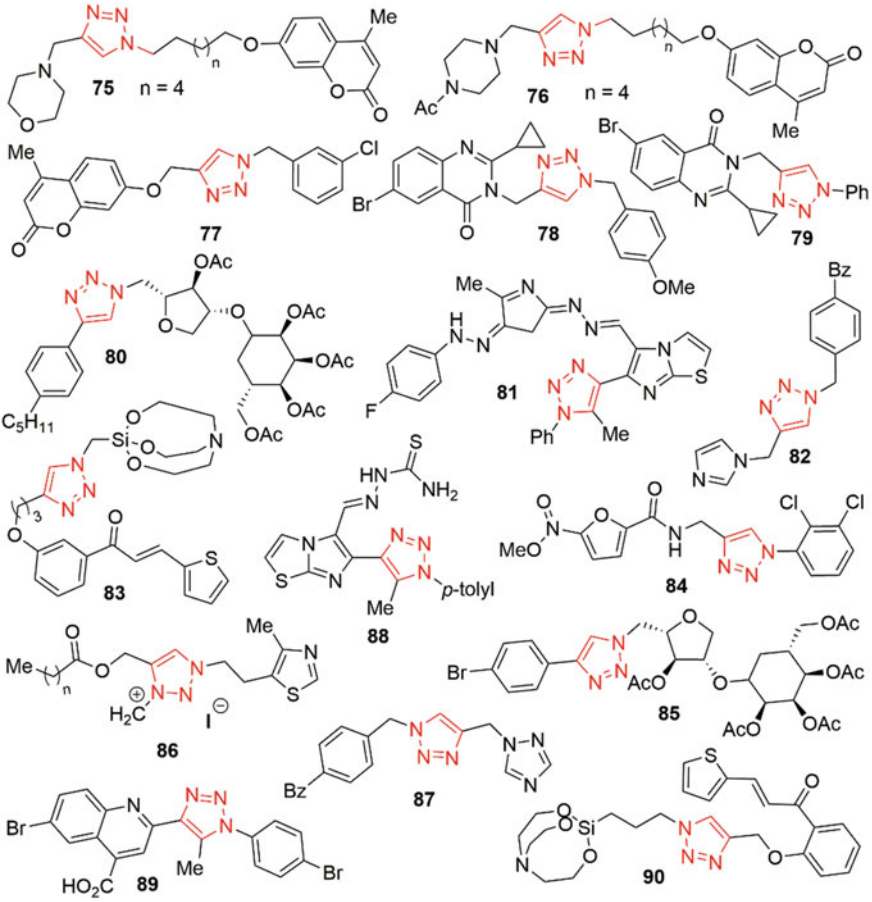


Fig. 8 Antimicrobial activity of 1,2,3-triazoles moieties [82–91]

7 Anti-viral Activity of 1,2,3-Triazole Derivatives

Viral toxicities are regarded as leading precarious infections, as they kill over million people yearly around the globe. Recently, coronavirus disease (COVID-19), an extremely infectious disease, killed more than 4 million people all over the world. In contrast, recent developments of anti-viral drugs show that there is a public health crisis to discover the extremely potent and ingenious agents. With this intent, several 1,2,3-triazole-based compounds were produced and evaluated for anti-viral action [92–98].

The compound **91** exhibited potency against influenza A replication which was higher to the standard drug ribavirin in terms of anti-viral activity as well as displayed human immunodeficiency virus type-1 reverse transcriptase (HIV-1 RT) activity

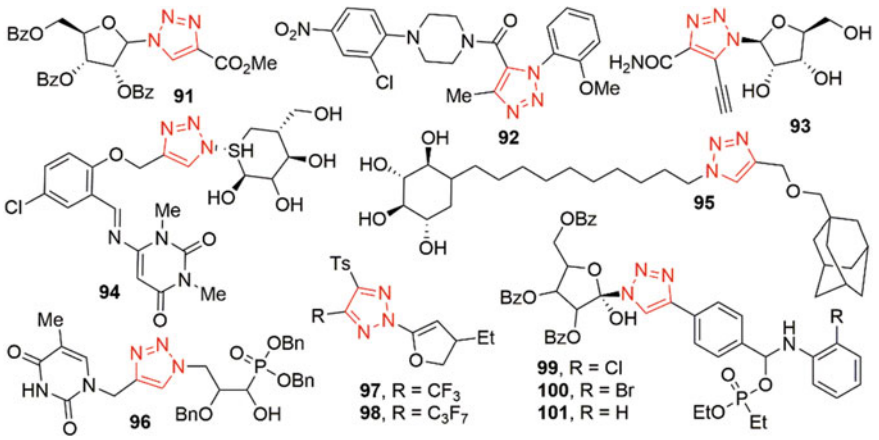


Fig. 9 1,2,3-triazoles moieties with anti-viral activity [92–98]

[92]. Indeed, analogue **92** showed powerful inhibitory action against the replication of H5N1 (RG14) (influenza a virus), amantadine-resistant A/WSN/33 (H1N1) and oseltamivir-resistant A/WSN/1933 (H1N1, 274Y) virus strains. In addition, 5-ethynyl nucleoside **93** showed anti-viral activities counter to most of the viruses [93]. In continuation, the interactivity of circulating tumour DNA (CT-DNA) with the sugar-triazoles was screened, revealed that the compound **94** can interrelate via groove binding with circulating tumour DNA (CT-DNA) [94]. In addition, longer alkyl chain compound **95** potentially abridged RNA copies multiplication, with 10 μM treatment diminish viral RNA [95]. Furthermore, phosphonate **96**, exhibited anti-viral action in MDCK (Madin Darby canine kidney cell cultures) counter to Influenza A H3N2 subtype [96]. Additionally, compounds **97** and **98** exhibited high selectivity indices (polymerase chain reaction (PCR) method) for the cytotoxic activity and anti-EBV activity [97]. However, compounds **99** and **100** exhibited diffident inhibition in contrast to respiratory syncytial virus (RSV) and compound **101** showed uncertain inhibition counter to Coxsackievirus B4 (Fig. 9) [98].

8 Summary/Conclusion

1,2,3-triazole and its derivatives are recognised as prosperous motifs in medicinal chemistry and biosciences. Moreover, excellent features of 1,2,3-triazole accelerate its broad spectrum of implementation from bioconjugation to material science. However, among the synthesised triazoles they resemble properties in which these scaffolds act as a linker, displaying CH-π interaction with enzymes. Nevertheless, the unique features of these moieties in the hybrid molecules make them a remarkable motif, a significant aspect in drug delivery and design. Scientists and researchers

around the globe make continuous efforts to improve and increase the 1,2,3-triazole-based chemistry, enabling the advancement of 1,2,3-triazoles derivatives with higher selectivity and lesser toxicity in future.

References

1. Praveena KSS, Murthy NYS, Pal S (2015) Synthesis and biological activities of 1,4-disubstituted-1,2,3-triazoles. J Chem Pharm Res 7:506–522
2. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Iynkkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C, Wilson M (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res 46:D1074−D1082
3. Haider S, Alam MS, Hamid H (2014) 1,2,3-Triazoles: scaffold with medicinal significance. Inflam Cell Signal 1:e95
4. Kappe CO, Eycken EVD (2010) Click chemistry under non-classical reaction conditions. Chem Soc Rev 39:1280–1290
5. Agalave SG, Maujan SR, Pore VS (2011) Click chemistry: 1,2,3-Triazoles as Pharmacophores 6:2696–2718
6. Khurshed B, Jiangyu Z, Aisaa HA (2019) 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: a recent overview. Bioorg Med Chem 27:3511–3531
7. Vatmurge NS, Hazra BG, Pore VS, Shirazi F, Chavan PS, Deshpande MV (2008) Synthesis and antimicrobial activity of beta-lactam-bile acid conjugates linked via triazole. Bioorg Med Chem Lett 18:2043–2047
8. Da Silva FDC, De Souza MCBV, Frugulhetti IIP, Castro HC, Souza SLDO, De Souza TML, Rodrigues DQ, Souza AMT, Abreu PA, Passamani F, Rodrigues CR, Ferreira VF (2009) Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. Eur J Med Chem 44:373–383
9. Cocklin S, Gopi H, Querido B, Nimmagadda M, Kuriakose S, Cicala C, Ajith S, Baxter S, Arthos J, Martin-Garcia J, Chaiken IM (2007) Broad-spectrum antihuman immunodeficiency virus (HIV) potential of a peptide HIV type 1 entry inhibitor. J Virol 81:3645–3648
10. Yu WJ, Rao Q, Wang M, Tian Z, Lin D, Liu XR, Wang JX (2006) The Hsp90 inhibitor 17-allylamide-17- demethoxygeldanamycin induces apoptosis and differentiation of Kasumi-1 harboring the Asn822Lys KIT mutation and down-regulates KIT protein level. Leukemia Res 30:575–582
11. Nahrwold M, Bogner T, Eissler S, Verma S, Sewald N (2010) "Clicktophycin- 52": a bioactive cryptophycin-52 triazole analogue. Org Lett 12:1064–1067
12. Fichtali I, Chraibi M, Aroussi FE, Ben-Tama A, Hadrami EME, Benbrahim KF, Stiriba SE (2016) Synthesis of some 1,2,3-triazoles derivatives and evaluation of their antimicrobial activity. Der Pharma Chem 8:236–242
13. Abdel-Wahab BF, Mohamed HA, Awad GEA (2015) Synthesis and biological activity of some new 1,2,3-triazole hydrazone derivatives. Eur Chem Bull 4:106–109
14. Kharb R, Sharma PC, Yar MS (2011) Pharmacological significance of triazole scaffold. J Enzyme Inhib Med Chem 26:1–21
15. Ferreira VF, da Rocha DR, da Silva FC, Ferreira PG, Boechat NA, Magalhães JL (2013) Novel 1H–1,2,3-, 2H–1,2,3-, 1H–1,2,4- and 4H–1,2,4-triazole derivatives: a patent review (2008–2011). Expert Opin Ther Pat 23:319–331
16. Sekhar DC, Rao DVV, Uppalla LK, Jha A (2017) Synthesis, molecular modeling and anticancer activity of novel 1,2,3-triazole hybrids-a click chemistry approach. J Chem Pharm Res 9:1–10
17. Prachayasittikul V, Pingaew R, Anuwongcharoen N, Worachartcheewan A, Nantasenamat C, Prachayasittikul S, Ruchirawat S, Prachayasittikul V (2015) Discovery of novel 1,2,3-triazole

derivatives as anticancer agents using QSAR and in silico structural modification. Springerplus 4:571
18. Zhang Z, Zhou L, Xie N et al (2020) Overcoming cancer therapeutic bottleneck by drug repurposing. Sig Transduct Target Ther 5:113
19. Odlo K, Hentzen J, Chabert JFD, Ducki S, Gani OABSM, Sylte I, Skrede M, Flørenes VA, Hansen TV (2008) 1,5-Disubstituted 1,2,3-triazoles as cis-restricted analogues of combretastatin A-4: synthesis, molecular modeling and evaluation as cytotoxic agents and inhibitors of tubulin. Bioorg Med Chem 16:4829–4838
20. Bathula SNP, Vadla R (2011) Bioactivity of 1,4-disubstituted 1,2,3-triazoles as cytotoxic agents against the various human cell lines. Asian J Pharm Clin Res 4:66–67
21. Salameh BA, Leffler H, Nilsson UJ (2005) 3-(1,2,3-Triazol-1-yl)-1-thiogalactosides as small, efficient, and hydrolytically stable inhibitors of galectin-3. Bioorg Med Chem Lett 15:3344–3346
22. Stefely JA, Palchaudhuri R, Miller PA, Peterson RJ, Moraski GC, Hergenrother PJ, Miller MJ (2010) N-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl) arylamide as a new scaffold that provides rapid access to antimicrotubule agents: synthesis and evaluation of antiproliferative activity against select cancer cell lines. J Med Chem 53:3389–3395
23. Philip S, Purohit MN, La KK, Eswar MS, Raizaday T, Prudhvi S, Pujar GV (2014) Design, synthesis and in vitro anti-cancer activity of novel 1,2,4-triazole derivatives. Int J Pharm Sci 6:185–189
24. Ashwini N, Garg M, Mohan CD, Fuchs JE, Rangappa S, Anusha S, Swaroop TR, Rakesh KS, Kanojia D., Madan V, Bender A, Koeffler HP, Basappa, Rangappa BKS (2015) Synthesis of 1,2-benzisoxazole tethered 1,2,3-triazoles that exhibit anticancer activity in acute myeloid leukemia cell lines by inhibiting histone deacetylases, and inducing p21 and tubulin acetylation. Bioorg Med Chem 23:6157–6165
25. Majeed R, Sangwan PL, Chinthakindi PK, Khan I, Dangroo NA, Thota N, Hamid A, Sharma PR, Saxena AK, Koul S (2013) Synthesis of 3-O-propargylated betulinic acid and its 1,2,3-triazoles as potential apoptotic agents. Eur J Med Chem 63:782–792
26. Yan S-J, Liu Y-J, Chen Y-L, Liu L, Lin J (2010) An efficient one-pot synthesis of heterocycle-fused 1,2,3-triazole derivatives as anti-cancer agents. Bioorg Med Chem Lett 20:5225–5228
27. Pokhodylo N, Shyyka O, Matiychuk V (2013) Synthesis of 1,2,3-triazole derivatives and evaluation of their anticancer activity. Sci Pharm 81:663–676
28. Penthala NR, Madhukuri L, Thakkar S, Madadi NR, Lamture G, Eoff RL, Crooks PA (2015) Synthesis and anti-cancer screening of novel heterocyclic-(2H)- 1,2,3-triazoles as potential anti-cancer agents. Med Chem Commun 6:1535–1543
29. Duan Y-C, Zheng Y-C, Li X-C, Wang M-M, Ye X-W, Guan Y-Y, Liu G-Z, Zheng J-X, Liu H-M (2013) Design, synthesis and antiproliferative activity studies of novel 1,2,3-triazole-dithiocarbamate-urea hybrids. Eur J Med Chem 64:99–110
30. Safavi M, Ashtari A, Khalili F, Mirfazli SS, Saeedi M, Ardestani SK, Ranjbar PR, Tehrani MD, Larijani B, Mahdavi M (2018) Novel quinazolin-4(3*H*)-one linked to 1,2,3-triazoles: synthesis and anticancer activity. Chem Biol Drug Des 92:1373–1381
31. Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti A, Batra SK (2012) Targeting the EGFR signaling pathway in cancer therapy. Expert Opin Ther Targets 16:15–31
32. Collin AA, Hubert P, Crémel G, Bennasroune A. Role of ErbB receptors in cancer cell migration and invasion. Front Pharmacol 6:283
33. Elamari H, Slimi R, Chabot GG, Quentin L, Scherman D, Girard C (2013) Synthesis and *in vitro* evaluation of potential anticancer activity of mono- and bis-1,2,3-triazole derivatives of bis-alkynes. Eur J Med Chem 60:360–364
34. Jiang B, Huang X, Yao H, Jiang J, Wu X, Jiang S, Wang Q, Lu T, Xu J (2014) Discovery of potential anti-inflammatory drugs: diaryl-1,2,4-triazoles bearing N-hydroxyurea moiety as dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase. Org Biomol Chem 12:2114–2127
35. Kim TW, Yong Y, Shin SY, Jung H, Park KH, Lee YH, Lim Y, Jung K-Y (2015) Synthesis and biological evaluation of phenyl-1H-1,2,3-triazole derivatives as anti-inflammatory agents. Bioorg Chem 59:1–11

36. Sarigol D, Uzgoren-Baran A, Tel BC, Somuncuoglu EI, Ozadali-Sari IKK, Unsal-Tan O, Okay G, Ertan M, Tozkoparan B (2015) Novel thiazolo[3,2-b]-1,2,4- triazoles derived from naproxen with analgesic/anti-inflammatory properties: synthesis, biological evaluation and molecular modeling studies. Bioorg Med Chem 23:2518–2528
37. Abdel-Megeed AM, Abdel-Rahman HM, Alkaramany GES, El-Gendy MA (2009) Design, synthesis and molecular modeling study of acylated 1,2,4-triazole-3- acetates with potential anti-inflammatory activity. Eur J Med Chem 44:117–123
38. Angajala KK, Vianala S, Macha R, Raghavender M, Thupurani MK, Pathi PJ (2016) Synthesis, anti-inflammatory, bactericidal activities and docking studies of novel 1,2,3-triazoles derived from ibuprofen using click chemistry. Springerplus 5:423–438
39. Paprocka R, Wiese M, Eljaszewicz A, Helmin-Basa A, Gzella A, Modzelewska-Banachiewicz B, Michalkiewicz J (2015) Synthesis and anti-inflammatory activity of new 1,2,4-triazole derivatives. Bioorg Med Chem Lett 25:2664–2667
40. Shafi S, Alam MM, Mulakayala N, Mulakayala C, Vanaja G, Kalle AM, Pallu R, Alam MS (2012) Synthesis of novel 2-mercapto benzothiazole and 1,2,3- triazole based bis-heterocycles: their anti-inflammatory and anti-nociceptive activities. Eur J Med Chem 49:324–333
41. Ahmadi F, Ghayahbashi MR, Sharifzadeh M, Alipoiur E, Ostad SN, Vosooghi M, Khademi HR, Amini M (2014) Synthesis and evaluation of anti-inflammatory and analgesic activities of new 1,2,4-triazole derivatives. Med Chem 11:69–76
42. Assis SP, da Silva MT, de Oliveira RN, Lima VL (2012) Synthesis and antiinflammatory activity of new alkyl-substituted phthalimide 1H-1,2,3-triazole derivatives. Sci World J 2012:925925
43. Singh RJ (2009) 1, 2, 3-Triazole derivatives as possible anti-inflammatory agents. Rasayan J Chem 2:706–708
44. Shaikh MH, Subhedar DD, Arkile M, Khedkar VM, Jadhav N, Sarkar D, Shingate BB (2016) Synthesis and bioactivity of novel triazole incorporated benzothiazinone derivatives as antitubercular and antioxidant agent. Bioorg Med Chem Lett 26:561–569
45. Gill C, Jadhav G, Shaikh M, Kale R, Ghawalkar A, Nagargoje D, Shiradkar M (2008) Clubbed [1,2,3] triazoles by fluorine benzimidazole: a novel approach to H37Rv inhibitors as a potential treatment for tuberculosis. Bioorg Med Chem Lett 18:6244–6247
46. Flieger J, Tatarczak-Michalewska M, Wujec M, Pitucha M, Swieboda R (2015) RPHPLC analysis and in vitro identification of antimycobacterial activity of novel thiosemicarbazides and 1,2,4-triazole derivatives. J Pharm Biomed Anal 107:501–511
47. Costa MS, Boechat N, Rangel EA, Silva FC, de Souza AMT, Rodrigues CR, Castro HC, Junior IN, Lourenco MCS, Wardell SMSV, Ferreira VF (2006) Synthesis, tuberculosis inhibitory activity, and SAR study of N-substitutedphenyl-1,2,3-triazole derivatives. Bioorg Med Chem 14:8644–8653
48. Kucukguzel I, Tatar E, Kucukguzel SG, Rollas S, Clercq ED (2008) Synthesis of some novel thiourea derivatives obtained from 5-[(4-aminophenoxy) methyl]-4-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones and evaluation as antiviral/anti-HIV and anti-tuberculosis agents. Eur J Med Chem 43:381–392
49. Shaikh MH, Subhedar DD, Nawale L, Sarkar D, Khan FAK, Sangshetti JA, Shingate BB (2008) (2015) 1,2,3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study. Med Chem Commun 6:1104–1116
50. Menendeza C, Gaua S, Lherbet C, Rodriguez F, Inard C, Pasca MR, Baltas M (2011) Synthesis and biological activities of triazole derivatives as inhibitors of InhA and antituberculosis agents. Eur J Med Chem 46:5524–5531
51. De P, Yoya GK, Constant P, Bedos-Belval F, Duran H, Saffon N, Daff M, Baltas M (2011) Design, synthesis, and biological evaluation of new cinnamic derivatives as antituberculosis agents. J Med Chem 54:1449–1461
52. Kumar KK, Seenivasan SP, Kumar V, Das TM (2011) Synthesis of quinoline coupled [1,2,3]-triazoles as a promising class of anti-tuberculosis agents. Carbohyd Res 346:2084–2090
53. Tehrani KH, Mashayekhi V, Azerang P, Minaei S, Sardari S, Kobarfard F (2015) Synthesis and antimycobacterial activity of some triazole derivatives–new route to functionalized triazolopyridazines. Iran J Pharm Res 14:59–68

54. Upadhayaya RS, Kulkarni GM, Vasireddy NR, Vandavasi JK, Dixit SS, Sharma V, Chattopadhyaya J (2009) Design, synthesis and biological evaluation of novel triazole, urea and thiourea derivatives of quinoline against Mycobacterium tuberculosis. Bioorg Med Chem 17:4681–4692
55. Shaikh MH, Subhedar DD, Nawale L, Sarkar D, Khan FAK, Sangshetti JN, Shingate BB (2015) 1,2,3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study. Med Chem Commun 6:1104–1116
56. Cassamale TB, Costa EC, Carvalho DB, Cassemiro NS, Tomazela CC, Marques MCS, Ojeda M, Matos MFC, Albuquerque S, Arruda CCP, Baroni ACM (2016) Synthesis and antitrypanosomastid activity of 1,4-diaryl-1,2,3- triazole analogues of neolignans veraguensin, grandisin and machilin G. J Braz Chem Soc 27:1217–1228
57. Adam R, Bilbao-Ramos P, Abarca B, Ballesteros R, González-Rosende ME, Dea-Ayuela MA, Estevan F, Alzuet-Piña G (2015) Triazolopyridopyrimidines: an emerging family of effective DNA photocleavers. DNA binding. Antileishmanial activity. Org Biomol Chem 13:4903–4917
58. Gontijo VS, Espuri PF, Alves RB, de Camargos LF, dos Santos FV, de Souza JWA, Marques MJ, Freitas RP (2015) Leishmanicidal, antiproteolytic, and mutagenic evaluation of alkyltriazoles and alkylphosphocholines. Eur J Med Chem 101:24–33
59. Daligaux P, Pomel S, Leblanc K, Loiseau PM, Cave C (2016) Simple and efficient synthesis of 5‘-aryl-5‘deoxyguanosine analogs by azide-alkyne click reaction and their antileishmanial activities. Mol Divers 20:507–519
60. Dwivedi P, Mishra KB, Mishra BB, Singh N, Singh RK, Tiwari VK (2015) Click inspired synthesis of antileishmanial triazolyl O-benzylquercetin glycoconjugates. Glycoconj J 32:127–140
61. Tahghighi A, Razmi S, Mahdavi M, Foroumadi P, Ardestani SK, Emami S, Kobarfard F, Dastmalchi S, Shafiee A, Foroumadi A (2012) Synthesis and anti-leishmanial activity of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines containing N-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] moieties. Eur J Med Chem 50:124–128
62. Porta EOJ, Carvalho PB, Avery MA, Tekwani BL, Labadie GR (2014) Click chemistry decoration of amino sterols as promising strategy to developed new leishmanicidal drugs. Steroids 79:28–36
63. Bakunov SA, Bakunova SM, Wenzler T, Ghebru M, Werbovetz KA, Brun R, Tidwell RR (2010) Synthesis and antiprotozoal activity of cationic 1,4-diphenyl-1H-1,2,3-triazoles. J Med Chem 53:254–272
64. Ferreira SB, Costa MS, Boechat N, Bezerra RJS, Genestra MS, Canto-Cavalheiro MM, Kover WB, Ferreira VF (2007) Synthesis and evaluation of new difluoromethyl azoles as antileishmanial agents. Eur J Med Chem 42:1388–1395
65. Corrales RCNR, de Souza NB, Pinheiro LS, Abramo C, Coimbra ES, da Silva AD (2011) Thiopurine derivatives containing triazole and steroid: synthesis, antimalarial and antileishmanial activities. Biomed Pharmacother 65:198–203
66. Daligaux P, Pome S, Leblanc K, Loiseau PM, Cavé C (2016) Simple and efficient synthesis of 5‘-aryl-5‘-deoxyguanosine analogs by azide-alkyne click reaction and their antileishmanial activities. Mol Divers 20:507–519
67. Guimaraes TT, Pinto MC, Lanza JS, Melo MN, Monte-Neto RL, Diogo EB, Ferreira VF, Camara CA, Valença WO, de Oliveira RN, Frézard F, da Silva Júnior EN (2013) Potent naphthoquinones against antimony-sensitive and resistant Leishmania parasites: synthesis of novel α- and nor-α-lapachone-based 1,2,3-triazoles by copper catalyzed azide-alkyne cycloaddition. Eur J Med Chem 63:523–530
68. Campo VL, Sesti-Costa R, Carneiro ZA, Silva JS, Schenkman S, Carvalho I (2012) Design, synthesis and the effect of 1,2,3-triazole sialylmimetic neoglycoconjugates on Trypanosoma cruzi and its cell surface transsialidase. Bioorg Med Chem 20:145–156
69. Dheer D, Singh V, Shankar R (2017) Medicinal attributes of 1,2,3-triazoles: current developments. Bioorg Chem 71:30–54
70. Gontijo VS, Espuri PF, Alves RB, Camargos LF, Santos FVD, Judice WAS, Marques MJ, Freitas RP (2015) Leishmanicidal, antiproteolytic, and mutagenic evaluation of alkyltriazoles and alkylphosphocholines. Eur J Med Chem 101:24–33

71. Holpuch A (2016) UN meeting tackles the “fundamental threat” of antibiotic-resistant superbugs. Guardian
72. Grange JM, Zumla A (2002) The global emergency of tuberculosis: what is the cause? J R Soc Health 122:78–81
73. Mady MF, Awad GAE, Jørgensen KB (2014) Ultrasound-assisted synthesis of novel 1,2,3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents. Eur J Med Chem 84:433–443
74. Kant R, Kumar D, Agarwal D, Gupta RD, Tilak R, Awasthi SK, Agarwal A (2016) Synthesis of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities. Eur J Med Chem 113:34–49
75. Singh H, Sindhu J, Khurana JM, Sharma C, Aneja KR (2014) Ultrasound promoted one pot synthesis of novel fluorescent triazolyl spirocyclic oxindoles using DBU based task specific ionic liquids and their antimicrobial activity. Eur J Med Chem 77:145–154
76. Jadhav RP, Raundal HN, Patil AA, Bobade VD (2015) Synthesis and biological evaluation of a series of 1,4-disubstituted 1,2,3-triazole derivatives as possible antimicrobial agents. J Saudi Chem Soc 21. https://doi.org/10.1016/j.jscs.2015.03.003
77. Ruddarraju RR, Murugulla AC, Kotla R, Tirumalasetty MCB, Wudayagiri R, Donthabakthuni S, Maroju R, Baburao K, Parasa LS (2016) Design, synthesis, anticancer, antimicrobial activities and molecular docking studies of theophylline containing acetylenes and theophylline containing 1,2,3- triazoles with variant nucleoside derivatives. Eur J Med Chem 123:379–396
78. Garudachari B, Isloor AM, Satyanarayana MN, Fun HK, Hegde G (2014) Click chemistry approach: regioselective one-pot synthesis of some new 8- trifluoromethylquinoline based 1,2,3-triazoles as potent antimicrobial agents. Eur J Med Chem 74:324–332
79. Aly MRES, Saad HA, Mohamed MA (2015) Click reaction based synthesis, antimicrobial, and cytotoxic activities of new 1,2,3-triazoles. Bioorg Med Chem Lett 25:2824–2830
80. Lv JS, Peng XM, Kishore B, Zhou CH (2014) 1,2,3-Triazole-derived naphthalimides as a novel type of potential antimicrobial agents: synthesis, antimicrobial activity, interaction with calf thymus DNA and human serum albumin. Bioorg Med Chem Lett 24:308–313
81. Nagender P, Reddy GM, Kumar RN, Poornachandra Y, Kumar CG, Narsaiah B (2014) Synthesis, cytotoxicity, antimicrobial and anti-biofilm activities of novel pyrazolo[3,4-*b*]pyridine and pyrimidine functionalized 1,2,3-triazole derivatives. Bioorg Med Chem Lett 24:2905–2908
82. Kushwaha K, Kaushik N, Lata Jain SC (2014) Design and synthesis of novel 2H-chromen-2-one derivatives bearing 1,2,3-triazole moiety as lead antimicrobials. Bioorg Med Chem Lett 24:1795–1801
83. Shaikh MH, Subhedar DD, Shingate BB, Khan FAK, Sangshetti JN, Khedkar VM, Nawale L, Sarkar D, Navale GR, Shinde SS (2016) Synthesis, biological evaluation and molecular docking of novel coumarin incorporated triazoles as antitubercular, antioxidant and antimicrobial agents. Med Chem Res 25:790–804
84. Vani KV, Ramesh G, Rao CV (2016) Synthesis of new triazole and oxadiazole derivatives of quinazolin-4(3H)-one and their antimicrobial activity. J Heterocycl Chem 53:719–726
85. Petrova KT, Potewar TM, Correia-da-Silva P, Barros MT, Calhelha RC, Ciric A, Sokovic M, Ferreira ICFR (2015) Antimicrobial and cytotoxic activities of 1,2,3-triazole-sucrose derivatives. Carbohydr Res 417:66–71
86. Abdel-Wahab BF, Khidre RE, Awad GEA (2016) Design and synthesis of novel 6- (5-methyl-1H-1,2,3-triazol-4-yl)-5-[(2-(thiazol-2-yl)hydrazono)methyl]imidazo[2,1-*b*]thiazoles as antimicrobial agents. J Heterocycl Chem 54:489–494
87. Fichtali I, Laaboudi W, Hadrami EME, Aroussi FE, Ben-Tama A, Benlemlih M, Stiriba SE (2016) Synthesis, characterization and antimicrobial activity of novel benzophenone derived 1,2,3-triazoles. J Mater Environ Sci 7:1633–1641
88. Singha G, Arora A, Rani S, Maurya IK, Aulakh D, Wriedt M (2016) Heteroaryl chalcone allied triazole conjugated organosilatranes: synthesis, spectral analysis, antimicrobial screening, photophysical and theoretical investigations. RSC Adv 6:82057–82081

89. Kamal A, Hussaini SMA, Sucharitha ML, Poornachandra Y, Sultana F, Kumar CG (2015) Synthesis and antimicrobial potential of nitrofuran-triazole congeners. Org Biomol Chem 13:9388–9397
90. Tejero R, López D, López-Fabal F, Gómez-Garcés JL, Fernández-García M (2015) (2015) Antimicrobial polymethacrylates based on quaternized 1,3-thiazole and 1,2,3-triazole side-chain groups. Polym Chem 6:3449–3459
91. Senthil S, Gopi R (2015) N-Substituted-1,2,3-triazoles: synthesis, characterization and antimicrobial activity studies. Der Pharma Chem 7:15–23
92. de Ferreira MLG, Pinheiro LCDS, Santos-Filho O, Pecanha MDS, Sacramento CQ, Machado V, Ferreira V, Souza TML, Boechat N (2014) Design, synthesis, and antiviral activity of new 1H–1,2,3-triazole nucleoside ribavirin analogs. Med Chem Res 23:1501–1511
93. Krajczyk A, Kulinska K, Kulinski T, Hurst BL, Day CW, Smee DF, Ostrowski T, Januszczyk P, Zeidler J (2014) Antivirally active ribavirin analogues—4,5- disubstituted 1,2,3-triazole nucleosides: biological evaluation against certain respiratory viruses and computational modelling. Antivir Chem Chemother 23:161–171
94. Hemamalini A, Singam ERA, Mudedla SK, Subramanian V, Das TM (2015) Design and synthesis of sugar-triazole based uracil appended sugar-imine derivatives—an application in DNA binding studies. New J Chem 39:4575–4582
95. Howe JD, Smith N, Lee MJR, Ardes-Guisot N, Vauzeilles B, Désiré J, Baron A, Blériot Y, Sollogoub M, Alonzi DS, Butters TD (2013) Novel imino sugar aglucosidase inhibitors as antiviral compounds. Bioorg Med Chem 21:4831–4838
96. Głowacka IE, Balzarini J, Andrei G, Snoeck R, Schols D, Piotrowska DG (2014) Design, synthesis, antiviral and cytostatic activity of ω-(1H–1,2,3-triazol-1-yl)(polyhydroxy)alkylphosphonates as acyclic nucleotide analogues. Bioorg Med Chem 22:3629–3641
97. Kanishchev OS, Gudz GP, Shermolovich YG, Nesterova NV, Zagorodnya SD, Golovan AV (2011) Synthesis and biological activity of the nucleoside analogs based on polyfluoroalkyl-substituted 1,2,3-triazoles. Nucleos Nucleot Nucleic Acids 30:768–783
98. Ouahrouch A, Taourirte M, Schols D, Snoeck R, Andrei G (2016) Design, synthesis, and antiviral activity of novel ribonucleosides of 1,2,3-triazolylbenzylaminophosphonates. Arch Pharm Chem Life Sci 349:30–41