IJPSR (2022), Volume 13, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 March 2022; received in revised form, 24 May 2022; accepted, 09 June 2022; published 01 December 2022

ADVANCEMENTS AND FUTURE PERSPECTIVES OF 1, 2, 3 TRIAZOLE SCAFFOLD AS PROMISING ANTIVIRAL AGENT IN DRUG DISCOVERY

Pavan Kumar D. Chopade * and Anwar Rafique Shaikh

M. C. E. Society's Allana College of Pharmacy, Azam Campus, Camp, Pune - 411001, Maharashtra, India.

Keywords:

1, 2, 3 Triazole, Scaffold, Antiviral, Antidepressant, Antihistaminic, Antioxidant

Correspondence to Author:
Pavan Kumar D. Chopade

Research Scholar,
M. C. E. Society's Allana College of Pharmacy, Azam Campus, Camp, Pune - 411001, Maharashtra, India.

E-mail: pavya111@gmail.com

ABSTRACT: Severe viral infections like Covid-19 are emerging now a day and are the common causes of human illness and death. Presently, we have a limited availability of antiviral chemotherapeutic agents to prevent and treat these infections, so it is the need of an hour to develop potential antiviral drugs against various harmful and fatal viral infections. A large quantity of research has been performed on 1,2,3 triazole and their derivatives, which has proved the promising antiviral activity of this heterocyclic nucleus. Among nitrogen-containing heterocyclic compounds, 1, 2, 3-triazoles are privileged structure motifs and received great attention in academics and industry. Even though absent in nature, 1, 2, 3-triazoles have found broad applications in drug discovery, organic synthesis, polymer chemistry, supramolecular chemistry, bioconjugation, chemical biology, fluorescent imaging, and materials science. 1, 2, 3 triazole nucleus is one of the most important and well-known heterocycle which is a common and integral skeleton of a variety of medicinal compounds like antidepressant, antihistaminic, antioxidant, antitubercular, anti-Parkinson, antineoplastic, antihypertensive, antimalarial, local anaesthetic, antianxiety, antiobesity and immunomodulatory agents, *etc*. 1, 2, 3 triazole emerged as a pharmacologically significant scaffolds due to its broad and potent activity against severe infections. This review primarily lays emphasis on the recent advancements in the synthesis and biological evaluation of 1, 2, 3 triazole derivatives as antiviral agents which may facilitate the development of more potent and effective antiviral agents.

INTRODUCTION: A virus is the smallest type of parasite to exist, usually ranging from 0.02 to 0.3μm in size, although some viruses can be as large as 1μm. They are about 1/100th of the size of bacteria [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(12).4805-18

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(12).4805-18

A viral particle or virion contains a single nucleic acid (RNA or DNA) core surrounded by a protein coat and sometimes enzymes required to initiate viral replication.

Viruses can only replicate within the cells of animals, plants, and bacteria and, as such, are referred to as obligate intracellular parasites. Viruses are not classified according to the illnesses they cause; instead, they are grouped into different families based on whether the nucleic acid is single- or double-stranded, whether a viral envelope is present, and their mode of replication.

Virionis the complete infectious virus particle, while Spheres, rods, filaments, bullets, rectangles, triangles, and elongated tubes are some of the shapes of viruses [2]. Martinus Beijerinck 1898 discovered the tobacco mosaic virus, and since 5,000 strains of viruses have been introduced and studied. Still, most types of viruses remain undiscovered [3, 4]. A virus cannot replicate alone. Viruses must infect cells and use components of the host cell to make copies of themselves. They cause damage to the host organism by killing the host cell in the process. Viruses are present everywhere on Earth. Scientist estimates that viruses outnumber bacteria by 10 to 1. Viruses infect all types of organisms, including animals, plants and bacteria, *etc*.[5] Because viruses don't have the same components as bacteria, they cannot be killed by antibiotics; only antiviral medications or vaccines can eliminate or reduce the severity of viral diseases, including AIDS, COVID-19, measles and smallpox. The pandemic nature of different viral diseases is reviewed here in short.

Hepatitis B virus (HBV) infection is an acute and chronic infection and a major health problem in men [6]. From the study, it is clear that 400 million people worldwide are chronic HBV carriers [7]. The clinical spectrum of HBV infection ranges from subclinical to acute symptomatic hepatitis or, rarely, fulminant hepatitis during the acute phase and from the inactive hepatitis B surface antigen (HBsAg) carrier state, chronic hepatitis of various degrees of histologic severity to cirrhosis and its complications during the chronic phase [8 9]. Nearly 15–40% of patients with chronic hepatitis B progress to cirrhosis and end-stage liver disease [10].

Ebola virus disease (EVD) is a dangerous viral disease with a fatality rate ranging from 30% to 90%. Ebola virus disease was first reported in the 1970s in Zaire (now the Democratic Republic of the Congo). Until 2013, most outbreaks occurred in the Central Africa region, including Zaire, Sudan, and Uganda. However, between March and October 2014, over 10000 cases of EVD have been recorded in West Africa, such as in Guinea, Liberia, Sierra Leone, and Nigeria. A few hospital or secondary infections of EVD have occurred in Spain and the United States of America. Ebola virus disease is presently one of the world's most feared diseases [11].

HIV/AIDS is a life-threatening disease. In 2019, about 38 million people worldwide were living with HIV, and 690,000 deaths had occurred in that year [12]. An estimated 20.6 million of these live in eastern and southern Africa [13]. Between the time that AIDS was identified (in the early 1980s) and 2019, the disease has caused 32.7 million deaths worldwide. HIV/AIDS is considered a pandemic, a disease outbreak that is present over a large area and is actively spreading [14].

COVID-19 (Coronavirus Disease-2019) is a life-threatening disease. Since December 2019, when Covid-19 emerged in the Hunan seafood market in Wuhan, South China, and rapidly spread worldwide, the virus outbreak has been declared a public health emergency of international concern by the World Health Organization (WHO). Throughout the world, the disease has caused varying degrees of illness. A patient shows various symptoms, usually fever, cough, sore throat, breathlessness, fatigue, and malaise, among others [15]. The case fatality rate (CFR) reflects the number of deaths divided by the number of diagnosed cases within a given time interval. Based on Johns Hopkins University statistics, the global death-to-case ratio is 2.2% (2,409,381/109,190,723) as of 16 February 2021 [16].

Viruses produce multiple copies of themselves on the host cell's machinery and metabolism and assemble in the cell. Various approaches have been made for the design of antiviral drugs; some of the approaches include:

- Inhibitors of Virus adsorption.
- Inhibitors of Virus–cell fusion.
- Inhibitors of Viral DNA polymerase, *e.g.*, Acyclovir, valaciclovir, ganciclovir.
- Inhibitors of Reverse transcriptase *e.g.,* NRTIs: zidovudine, didanosine.
- Inhibitors of Acyclic nucleoside phosphonates *e.g.*, cidofovir, tenofovir.
- Inhibitors of processes associated with viral RNA synthesis.
- Inhibitors of Viral protease *e.g.,* saquinavir, ritonavir, indinavir.

- Inhibitors of Viral neuraminidase. *e.g.* Zanamivir, oseltamivir.
- Inhibitors of IMP dehydrogenase. *e.g.* Ribavirin.
- Inhibitors of S-adenosylhomocysteine hydrolase [17].

Drugs and organic compounds contain numerous scaffolds and structures. A ring system of structure is usually seen in these compounds. Heterocyclic compounds are also rung compounds made up of atoms of carbon atoms and at least one other element like N, S, P or O [18]. About half of the known organic compounds have structures that incorporate at least one heterocyclic component in them. So many heterocyclic compounds containing sulphur, nitrogen, and oxygen have been under investigation for a long time because of their important medicinal properties [19]. The largest and highest diversity group from heterocycles are the heterocyclic compounds containing five-membered rings with one nitrogen as heteroatom. Pyrrole, furan or thiophene are heterocyclic ring systems formed by substituting one or more of the CH groups by sp^2-hybridized nitrogen, oxygen, and sulfur. Heterocyclic groups like diazoles (pyrazole and imidazole), triazoles (1,2,3-and1,2,4-triazole) and tetrazolesrings are formed by changing number and positions of nitrogen atoms in the ring resulting in the structural diversity of heterocyclic compounds. Several medicinal agents and natural products contain heterocyclic compounds as common and integral structural feature components and possess a wide range of applications, e.g. pharmaceuticals, agrochemicals, and veterinary products [20].

Triazoles like 1,2,3-triazole, 1,2,4-triazole, benzotriazole, triazolopyrimidine **Fig. 1** and their derivatives are the popular heterocyclic compounds and drugs in the pharmaceutical industry. Many drugs marketed currently are based on triazoles, for example, Itraconazole, Voriconazole, and Fluconazole, as shown in **Fig. 2.** The favorable properties of 1, 2, 3-triazole rings are moderate dipole character, hydrogen bonding capability, rigidity, and stability under in vivo conditions, responsible for their enhanced biological activities [21-24]. Thus, the role of 1,2,3-triazole has become increasingly important in designing a new class of structural entities of medicinal importance.

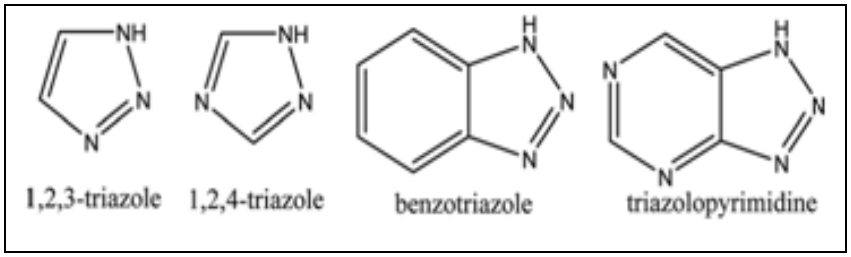


FIG. 1: THE STRUCTURE OF PHARMACEUTICALLY ACTIVE TRIAZOLE MOIETIES

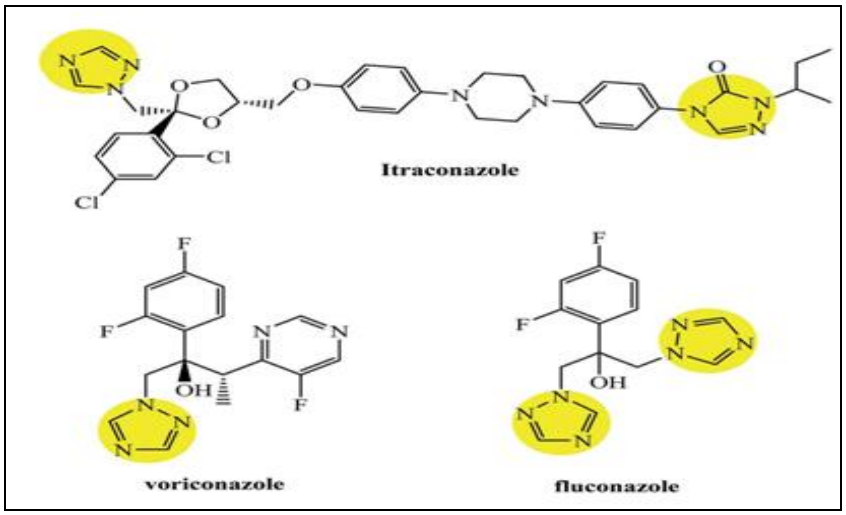


FIG. 2: THE STRUCTURES OF ITRACONAZOLE, VORICONAZOLE AND FLUCONAZOLE CONTAINING TRIAZOLE MOIETIES

1,2,3-triazoleis organic heterocyclic compound containing a five-membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions, also known as pyrrodiazole. Triazoles occur in **Fig. 3** as a pair of isomeric chemical compounds 1,2,3-triazole (1) and 1,2,4-triazole (2). 1,2,3-triazole and their derivatives are mostly synthesized by1,3-dipolar cycloaddition of wide variety of organic azides XN3 (X= alkyl, vinyl, aryl, acyl, arene, sulphonyl, *etc*.) to acetylenes, Einhorn–Brunner reaction , Pellizari reaction, reaction of azides with enolate anions, enol ethers, enamines and alphaacyl phosphorus ylides and azide addition reactions by the oxidative cyclization by copper(II) salts of the bis-phenyl hydrazones of 1,2-diketones [25 26].

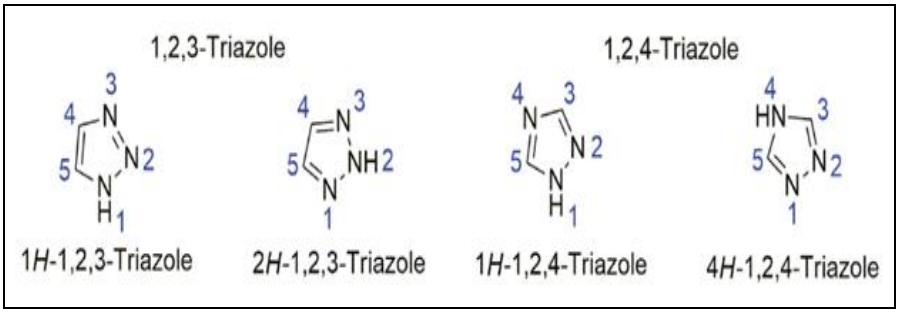
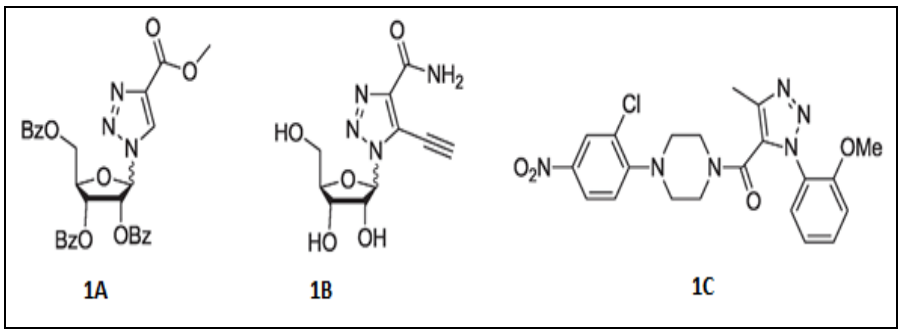


FIG. 3: MOLECULAR SCAFFOLD OF 1,2,3-TRIAZOLE AND 1,2,4-TRIAZOLE

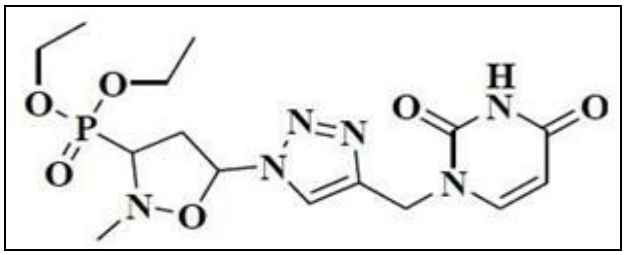
Antiviral Activity Profile: Viruses infect an organism's body and cause viral diseases. Nowadays, vaccines and antiviral drugs are used to treat viral diseases, but advances of novel viruses create health risk worldwide.

Hence the discovery of newer antiviral agents is of medicinal interest. Boechat *et al.* reported the synthesized and studied antiviral activity of 1,2,3-triazole nucleoside ribavirin analogs. First synthesized compound 1Adisplayed potent activity with IC_{50} values 14 and 3.8 μM for Influenza A and reverse transcriptase (RT) from human immunodeficiency virus type 1 (HIV-1 RT), respectively [27]. Zeidler *et al.* synthesized and screened the biological activities of Ribavirin analogues 4,5-disubstituted 1,2,3-triazole nucleosides.

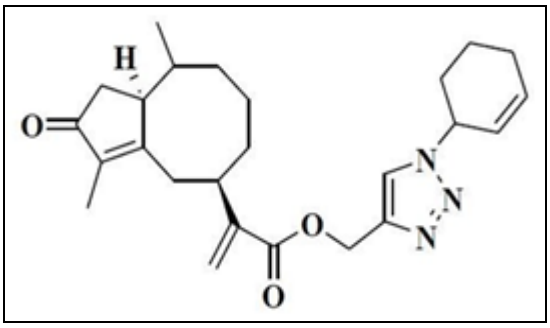
5-ethynyl nucleoside 1Bhad shown effective antiviral activity against influenza A (H1N1, H3N2 and H5N1), influenza B, measles and respiratory syncytial viruses [28]. Cheng *et al* synthesized 1, 2, 3-triazole – 4 - carboxamide derivatives and targeted virus nucleoprotein for anti-influenza drug development. The compound 1C inhibited the replication of various H_3N_2 and H1N1 influenza a virus strains with IC_{50} values ranging from 0.5 to 4.6 μM [29].



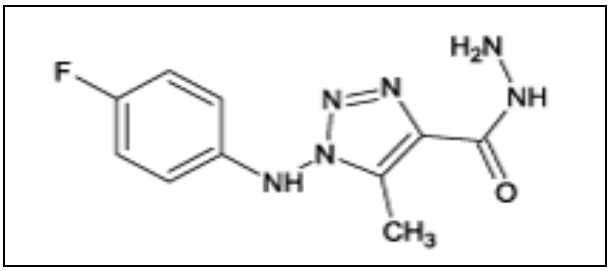
Piotrowska *et al.* studied the synthesis of novel isoxazolidine nucleotide analogues with a 1, 2, 3-triazolenucleus. The synthesized 1, 2, 3-triazole based isoxazolidine phosphonate derivatives were evaluated for antiviral activity. Compound depicted below showed promising *in-vitro* activity against variety of DNA and RNA viruses [30].



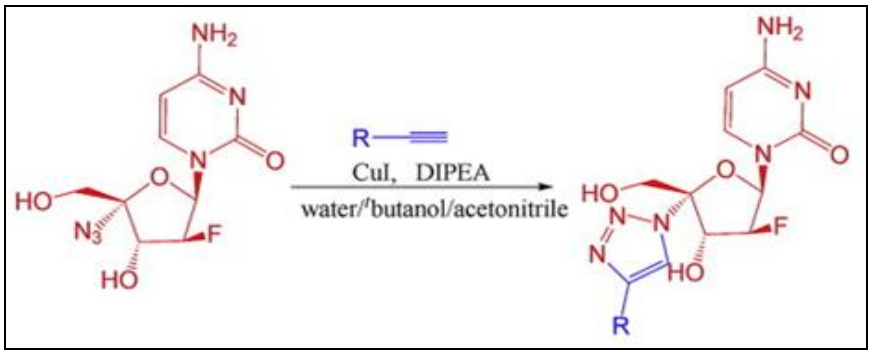
HeYW *et al* reported the synthesis of novel 1, 2, 3-triazole-containing rupestonic acid derivatives and carried out biological evaluation for their antiviral activity against influenza virus using oseltamivir and ribavirin as the standard drug. Compound depicted below showed significant activity against influenza virus [31].



Jordao *et al.* reported the evaluation ofantiviral activity of new N-amino-1,2,3-triazole derivatives, 1-(substituted- phenylamino)-5-methyl-1*H*-[1,2,3]-triazole – 4 - carboxylic acidethylesters and 1-(4-substituted - phenylamino) – 5 – methyl - 1*H*-[1, 2, 3]-triazole-4-carboxylic acid hydrazides on Cantagalo virus replication. Significant antiviral effectis exhibited by 1-(4-Fluoro-phenylamino)- 5-methyl - 1 *H* -[1, 2, 3] - triazole – 4 - carboxylic acidhydrazide [32].



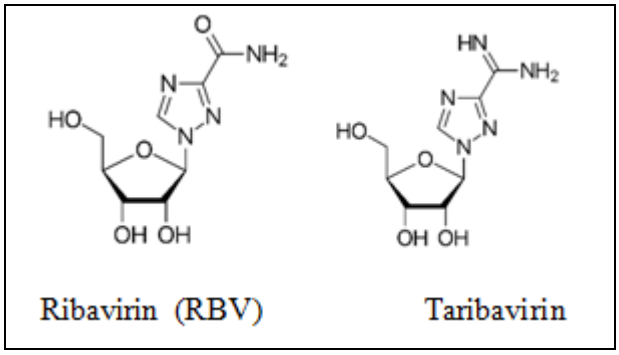
1-(4-fluro-phenylamino)-5- methyl-1*H*-[1, 2, 3]-triazole-4-carboxylic acid hydrazide. Wu J. *et al.* studied the first highly efficient synthesis and *in-vitro* anti-HIV-1 activity of novel 40sdN analogs with 1, 2, 3-triazole moiety nucleus at the 40-position through a CUAAC reaction. These compounds exhibited potent anti-HIV-1 activity without significant cytotoxicity at the highest tested concentration up to 25 mM. In the biological evaluation, some compounds were found extremely potent against HIV-1 wide-type strain without obvious cytotoxicity and merits further development as an anti-AIDS clinical trial candidate [33].



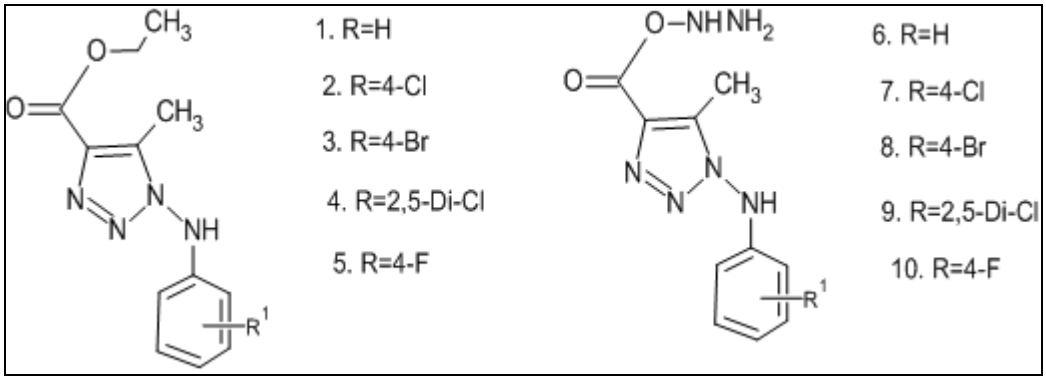
Ribavirin and Taribavirin are 1, 2, 3 triazole derrivatives antiviral drugs which are useful agents against a number of DNA and RNA viruses. They are used in severe respiratory syncytial virus infection, hepatitis C infection and other viral infections like West Nile virus and dengue fever [34 35].

Reporteddata depicts that ribavirin may have useful activity againstmany viruses of interest, including avian influenza, hepatitis B, polio, measles, canine distemper and smallpox [36]. Now a days Ribavirinis ideal treatment for a variety of viral hemorrhagic fevers, including Lassa fever, Crimean-Congo hemorrhagic fever and Hanta virus infection [37].

Taribavirin or viramidine is an antiviral drug which is in Phase III clinical human trials, but not approved till now for pharmaceutical use. It is a pro-drug of Ribavirin, active against a number of DNA and RNA viruses. Taribavirin has better liver-targeting than RBV and has a shorter life in the body due to less penetration and storage in red blood cells. Taribavirin is the choice of drug for viral hepatitis syndromes in which Ribavirin is active. This include hepatitis C and hepatitis B and yellow fever. Taribavirin is as active against influenza as Ribavirin in animal models, with slight less toxicity, so it may also eventually replace Ribavirin as an anti-influenza agent [38].

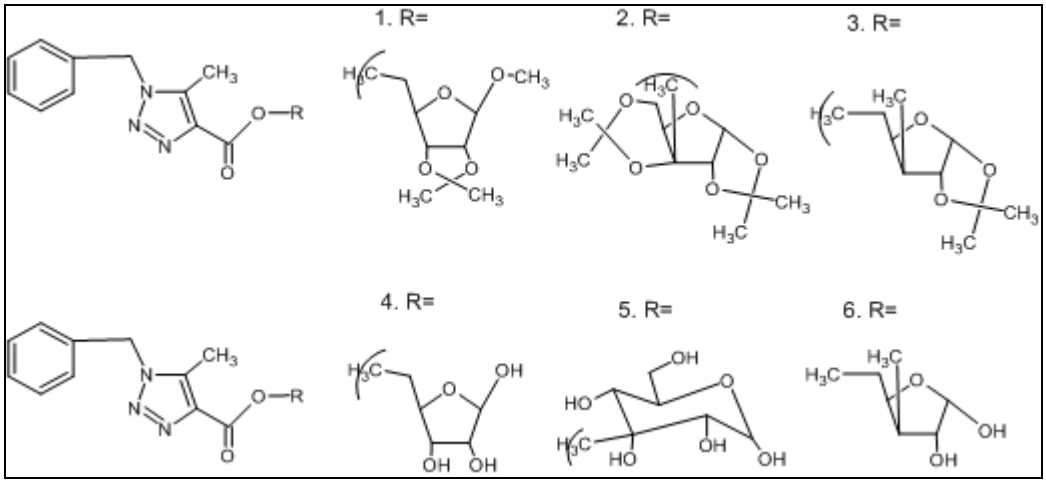


Jordao *et al* reported Antiviral activity of new N-amino-1,2,3-triazole derivatives (01-10), 1-(substitutedphenylamino)-5- methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid ethyl esters, (01-05) and 1-(4-substituted-phenylamino)-5- methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid hydrazides (6-10) on replication of Cantagalo virus in BSC-40 cells. Out of the ten compounds tested, compounds 3, 4and 10inhibited the formation of viral plaques by more than 30% at 50 mM after 48 hours post-infection and treatment. It is found that Compound 3had higher activity than the less lipophilic, unsubstituted compound 1. At a higher dose level 100 mM, compound 3 induced 84.62% inhibition of viral plaque formation but found toxic to the cells, alteringcell morphology and reducing cell viability to 52.6%. Compound 4, the dichloro derivative had a greater activity than the monochloro compound 2. Except for compound 5, the change from a 4-carbethoxy- triazole (1-4) to the corresponding acylhydrazides (6-9) resulted in a decreasing inhibitory response on Cantagalo virus replication. In case of compound 10, the electronic with drawing effect of fluorine group and the hydrogen donor and accceptor functionalities of the acylhydrazide moiety increased its biological activity. Activity of 4-carbethoxy-triazole 4 and acylhydrazide 10on yield of infectious virus particles were then studied after 24 hours post-infection and treatment. Both compounds inhibited virus progeny production by more than 55% at 50 mM. Moreover, using the neutral red assay to evaluate cellular toxicity, it was observed that 60% of the cells were viable when treated with the derivative 4at 50 mM for 24 hours. With the same concentration, compound 10generated 10% of non-viable cells after 24 hours of treatment and inhibited the yield of infectious virus particles by approximately 55%. Doses higher than 100 mM were toxic to BSC-40 cells, although at this concentration, the virus yield was inhibited by nearly 80% with only 30% of non- viable cells. In the presence of compound 10 the accumulation of viral proteins during infection was also inhibited. Western Blots technique used with antibodies to detect viral structural proteins, revealed normal levels of protein accumulation in infected cells treated with 0.5% DMSO (control). Virus proteins were not detected in mock-infected cells, as expected. Increasing concentrations of drug 10 gradually reduced the accumulation of virus proteins, reaching 71.2% inhibition at 100 mM, as determined by densitometric analysis of the blots. The cellular protein a-tubulin was detected to control total protein loading and normalization for the densitometric analysis. Hence drug structure 10 was proved to be a great potential as a lead structure with anti-cantagalo virus activity that can be used to develop new derivatives [39, 40].

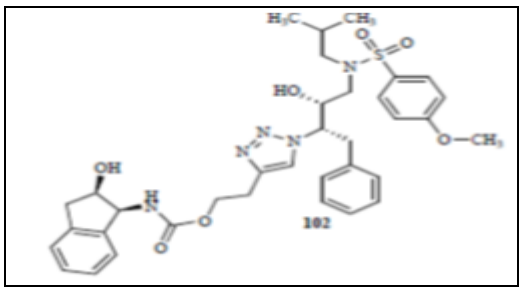


Da Silva *et al* reported the synthesis of two new triazole classes(1-6), including several 1-benzyl-1*H*-1,2,3-triazoles, which is bound to carbohydrate templates and explained their *in-vitro* inhibitory profile at different concentrations (0.01-50 µM) against HIV-1 RT by using recombinant HIV-1 enzyme and AZT as antiviral standard. Initially, all compounds were tested at 50 µM.

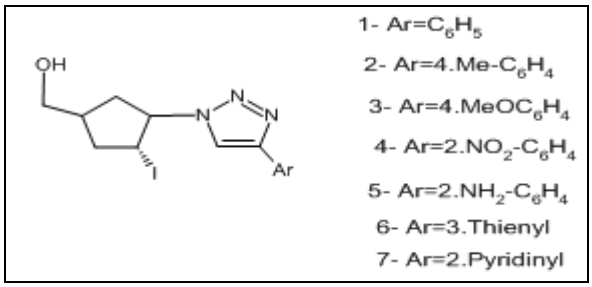
All compounds showed HIV RT inhibition to some degree. It is found that derivatives with the protected carbohydrate (1-3) shown an inhibitory profile greater than compounds 4-6 containing unprotected carbohydrate groups. Significantly, compounds 1-3produced the highest inhibitory values (63-65%) at 50 µM. The determination of the IC50 of the most active compounds against HIV-RT (1= 2.2 ± 0.8 µM, 2= 5.0 ± 0.5 µM and3= 1.98 ± 0.4 µM) shown values for these compounds higher than AZT, but similar to DDC (zalcitabine) and lamivudine and lower than DDI (didadosine). Hence it is concluded that for generating new anti-HIV-RT compounds, triazoles compounds 1-3may be considered as prominanat lead molecules for further synthetic and biological exploration [41].



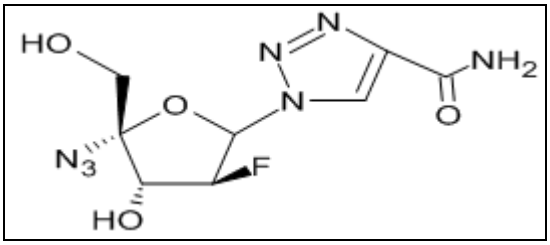
Giffin *et al* studied that a copper (I)-catalyzed 1,2,3-triazole derivatives shown to be potently effective against WT protease (IC_{50} = 6.0 nM), has low nM activity (IC_{50} = 15.7 nM) against the multidrug-resistant 6X protease mutant. This compound displayed greater activity towards WT and 6X HIV-1 in the evaluation of viral replication. While structural studies of bound to WT and mutant proteases shown a prominamnt change in binding mode in the mutants, the compound crystal structure showed nearly identical interactions in the WT protease complex which provide the basis for new inhibitors to target WT and multidrug resistant viruses [42].



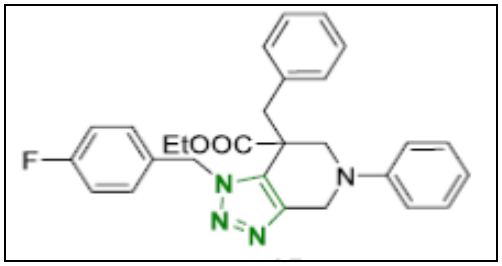
Perez-Castro *et al* reported the synthesis of 4-aryl-1, 2, 3 triazolo - 2', 3 '- dideoxy - 2' – iodocarba-nucleosides (1-7) and tested against varicella-zoster virus (TK+VZV, thymidine kinase positive strain and TK-VZV, thymidine kinase-deficient strain) and cytomegalovirus (CMV Davis strain) in HEL cells. Nearly all the compounds didn't show any specific antiviral activity (*i.e.*, minimal antiviral effective concentration 5-fold lower than minimal cytotoxic concentration) against any of the viruses in the assay systems used. Still, compound 1which exhibited inhibitory potential against TK+VZV (EC_{50} =4.5 µgmL-1) [43].



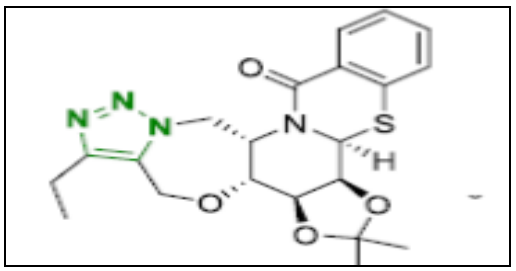
Liu *et al* synthesizeda 1,2,3-triazole scaffolds with 4- monosubstituted 2′-deoxy-2′-β-fluoro-4′-azido-β-D-arabinofuranosyl- and evaluated for its Anti-hepatitis B virus (HBV) properties. It is found that this triazole derivative had greater antiviral activity and promising potential against the lamivudine-resistant HBV mutants, which were also screened against HBV-infected duck models. The results showed that serum (67.4%) and liver duck-HBV DNA levels (53.3%) decreased after treatment with this molecule [44].



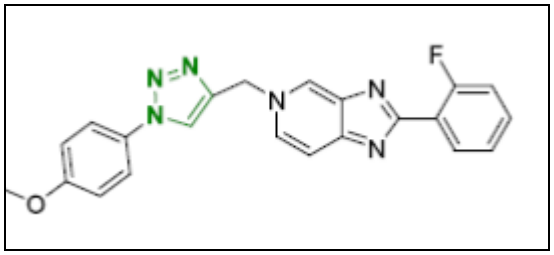
Karypidou *et al.* explained a series of fused 1,2,3-triazole heterocycles, and their antiviral properties have been explored. All synthesized hybrids were tested against several types of viruses such as HIV (types 1 and 2), herpes simplex viruses (types 1, 1 TK- and 2), adenovirus-2, coronavirus, and vaccinia virus and values were compared with the appropriate positive control drugs (zidovudine, brivudine, cidofovir, ganciclovir, acyclovir, alovudine, and Urtica dioica agglutinin and zalcitabine). Although antiviral assays indicated that the majority of compounds had slight or no activity against selected viruses, but drugdepicted below with an EC50 value of 8.95 μM was an averagely active compound against the human coronavirus (229E), but displayed nearly 50-fold lower inhibitory potency than Urtica dioica agglutinin (EC_{50}=0.2 μM) [45].



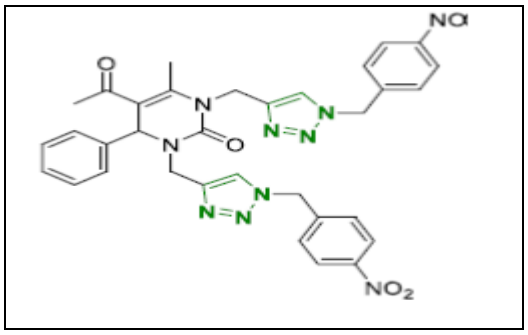
Yan L *et al.* reported the synthesis of pentacyclic iminosugar compounds by fusing triazole [5,1-c] [1,4] oxazepine scaffolds and evaluated their HIV reverse-transcriptase inhibitory activity. All synthesized compounds shown inhibitory activity against reverse transcriptase. But below-given drug was identified as a lead compound which has an IC_{50} value of 0.69 μM against enzyme reverse-transcriptase [46].



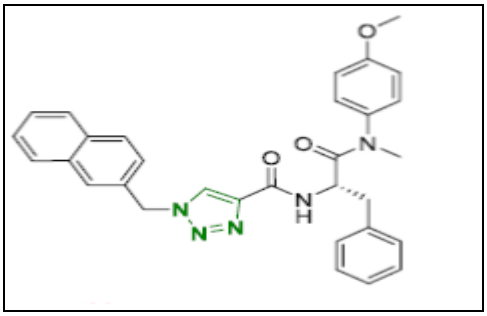
Liu Mreported synthesis by replacing the pyridazine moiety with a 1, 2, 3-triazole ring withpotential non-nucleoside inhibitory activity against hepatitis C virus (HVC) NS5B .Below given drug showed an EC_{50} of 1.163 nM and a CC50 > 200 nM in a cell-based HCV replicon system experiments, with respect to potency and pharmacokinetics [47].



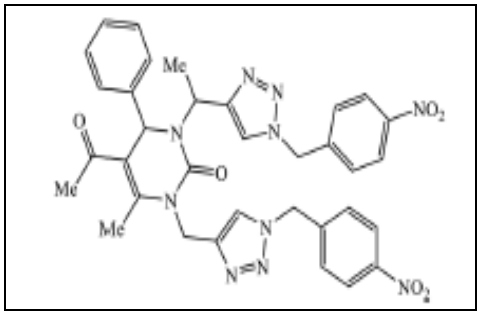
Kaoukabi H *et al* synthesized hybrid molecules containing triazole and dihydropyrimidinone rings *via* Huisgen azide-alkyne cycloaddition and were evaluated against human varicella-zoster virus activity. Below given drug demonstrated promising antiviral activity on TK+ varicella-zoster virus (VZV) strain with an EC50 of 3.6 μM, which decreased to 7.8 μM against the TK- strain. It is also found that the replacement of the benzyl fragment by 4-NO_2-benzyl increased the antiviral activity against TK+ VZV strains and considerably reduced the cell growth inhibition [48].



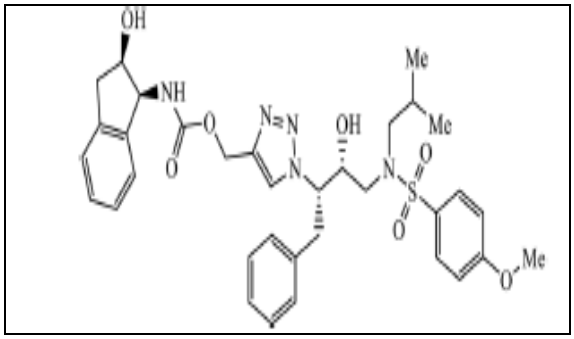
Wu G *et al.* synthesized novel 1,2,3-triazole-phenylalanine derivatives by CuAAC, and antiviral activity is checked against HIV-1 CA protein inhibitors.Below mentioned drug showed superior anti-HIV-1 potency (EC50=4.33 μM, SI > 13.33), which was equal to that of the HIV-1 capsid inhibitor 2-methyl-*N*-[(1*S*)-2-(methylphenylamino) -2-oxo-1-(phenylmethyl) ethyl] - 1*H* – indole - 3-acetamide (EC50=5.95 μM, SI > 11.85). This drug exhibited antiviral activity in the early and late stages of HIV-1 replication and interacted strongly with recombinant HIV-1 CA [49].



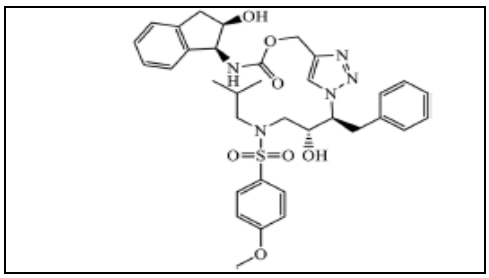
H. Kaoukabisynthesized 1, 2, 3-Triazole linked dihydropyrimidinone hybrid and checked antiviral activity against VZV, which is the causative agent for chickenpox. For TK +VZV the $EC_{50}$was 3.62 and For TK -VZV the $EC_{50}$was 3.62. This drug showed good antiviral activity against VZV [50].



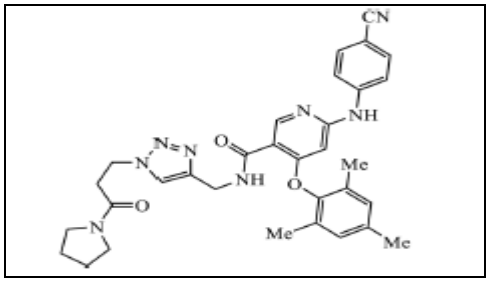
A. Brik *et al* reported that the activity of 1, 2, 3-triazolyl compounds to act as peptide surrogates, which is used as anti-HIV agent, is largely prominent and has very high activity against wild type and mutant HIV-1 proteases. It is found that crystallographic studies indicate the position of this inhibitor is similar to that of amprenavir and 1,2,3-triazole is a suitable scaffold of the peptide group. It is observed that 1,2,3- triazole is an effective replacement for a peptide group in the HIV-1 protease inhibitors, thus leading to high activity [51].



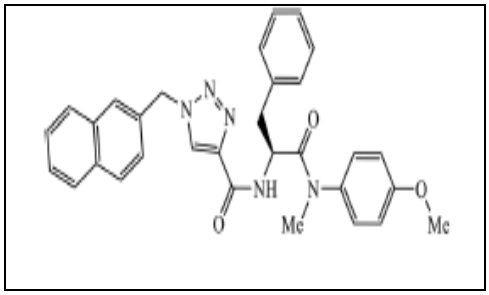
M. J. Giffinreported that 1,2,3-triazole derivatives have the potential to act as anti-HIV-1 protease inhibitor, with high activity of this compound against wild type protease [(IC50) 6.0 nm]. 1,2,3-triazole derivatives interact with selected residues and maintain hydrogen bonding to main chain atoms and lead to high activity [52].



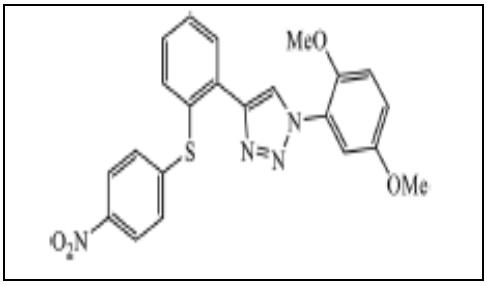
Tian *et al.* synthesized derivatives of diarylnicotinamide 1,4-disubstituted 1,2,3-triazoles with good anti-HIV1 activity against wild type HIV-1 and mutant HIV-1 strains in MT-4 cells. Activity evaluation against many strains including IIIB, K103N + Y181C, L100I, K103N, E138K, Y181C, Y188L, and F227L + V106A. It is found that the presence of nitro and cyano group at the 3 position on benzyl ring as shown in the molecule increases the activity of the compound against HIV-1 [53].



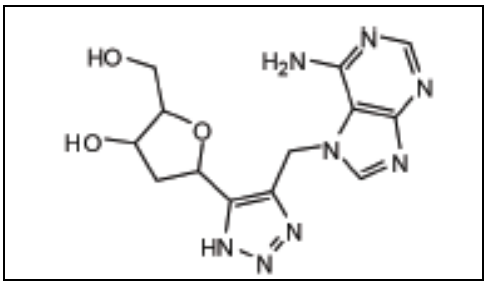
G. Wu *et al* synthesized phenylalanine derivatives by click chemistry exhibit excellent anti-HIV activity. Presence of b-substituted naphthalene, which is directly bound to triazole offers a very high activity against HIV-1 NL4-3 strain with much lesser toxicity. The results conclude that It potentially has two different binding modes with the HIV-1 CA monomer, which has implications for the precise manner of CA protein inhibition in each of the discrete stages of replication [54].



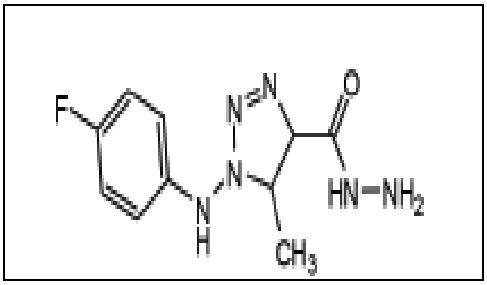
I. Mohammed *et al.* reported the synthesis of 1,2,3-triazoles along with amide bioisosteres and found effective anti-HIV against H9 cells. Different substituents attached to the benzyl ring are responsible for these compounds' activity. It has particularly high activity against the H9 cell line because of the presence of methoxy and nitro groups on two different benzyl rings [55].



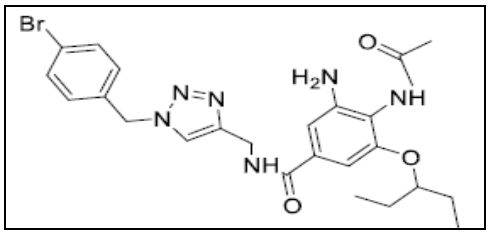
Hluhanich R *et al.* synthesized various derivatives of trisubstituted triazoles, and they were acting as inhibitors of reverse transcriptase, and below-given compound with the difference in thio group position were found most active compounds [56].



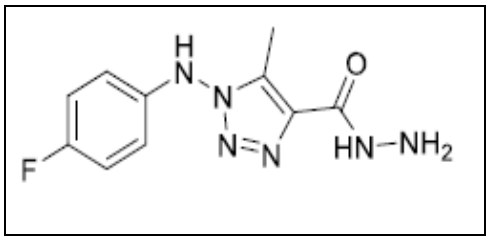
Cheng ZY *et al* reported the synthesis of N-amino-1,2,3-triazole derivatives.IR characterized all derivatives, 1H and 13C spectroscopy and elemental analysisand were exhibited prominent antiviral activity against cantalago virus [57].



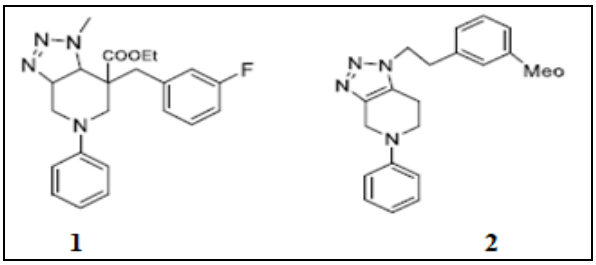
Ju *et al.* carry out the synthesis of 1,2,3-triazole oseltamivir analogues and checked antiviral activity against three different strains (H5N1, H5N2, H5N6) in both enzymatic assay and cellular assay. It has been found that the compound depicted below exhibited broad-spectrum antiviral activity with IC_{50} values 0.12 μM, 0.049 μM, and 0.16 μM against H5N1, H5N2, H5N6 [58].



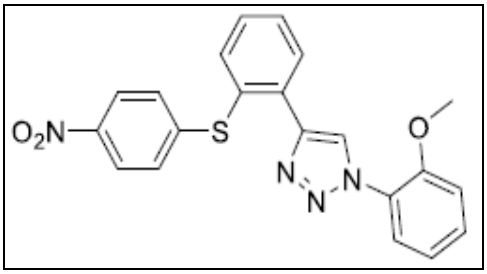
Jordao *et al.* reported synthesizing a novel series of N-amino- 1,2,3-triazole compounds and evaluated their antiviral activity against the Cantagalo virus. All compounds were shown activity, but the given below drug showed excellent antiviral activity [59].



Karypidou *et al.* reported the synthesis ofseveral 1,2,3- triazole derivatives as a potential antiviral agent. All the synthesized compounds were screened against a variety of viruses (HIV-1, HIV-2, vaccinia virus, adenovirus-2, and coronavirus) in HEL cells and their antiviral inhibitory activity was compared with standard drugs. Among all the cderrivatves, compounds depicted below 1 (EC_{50} = 8.95 μM) and 2 (EC_{50} = 8.90 μM) exhibited the moderate activity against human coronavirus [60].



Mohammed *et al.* synthesized 1,2,3-triazole compounds as amide bioisosteres and evaluated for their antiviral activity against H9 and MT4 cells. It is observed that the 1,4- disubstituted-1,2,3-triazole based derivatives were found to have no activity against MT4 cells and significant anti-HIV activity against only H9 cells (IC_{50} = 1.2 μM in H9 cells) [61].



R. Takhampunya reported the synthesis 1,2,3-triazole compounds and their biological activity against West Nile virus (WNV) and Dengue virus (DENV). Current efforts towards this end target approaches either through the nucleoside triphosphate biosynthesis as exemplified by mycophenolic acid (MPA), ribavirin and 6-azauridine, or viral proteins including both the helicase and the protease activities of NS3, the RNA-dependent RNA polymerase and the MTase functions of NS5 [62, 63].

S.K.V. Vernekar *et al* synthesized and studied 50-silylated 30- 1,2,3-triazolilyl thymidine bioisosteric scaffold derived from 30-azidothymidine (AZT) consistently and their selectively inhibiting WNV and DENV at low micromolar concentrations without inhibiting HIV or any other viruses tested. Structure activity study showed that both the 50-silyl protecting the group and the 30-bulky substituent are essential and turns on the antiviral activity against WNV and DENV which was confirmed through a plaque assay where viral titer reduction was observed in the presence of selected compounds displayed below.

Molecular modeling and competitive binding assay suggested that these compounds likely confer antiviral activity via binding to methyltransferase (MTase) [64].

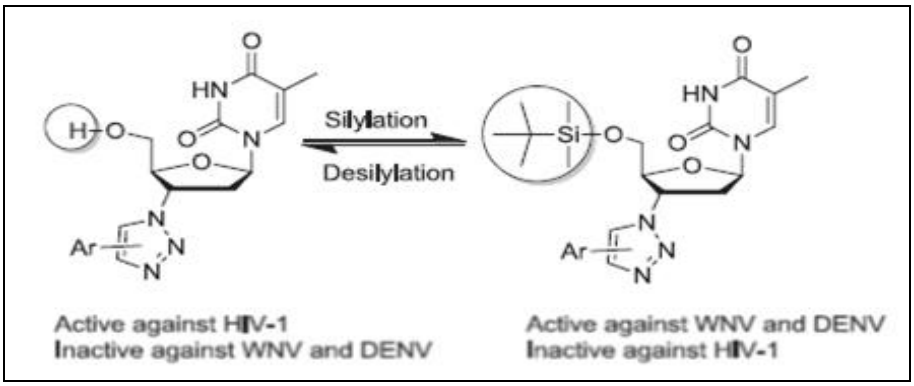
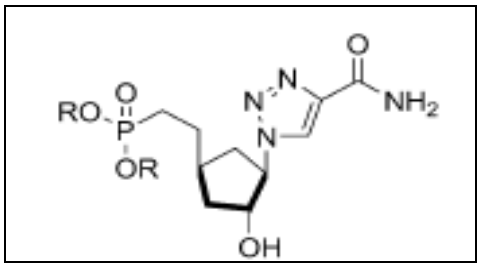
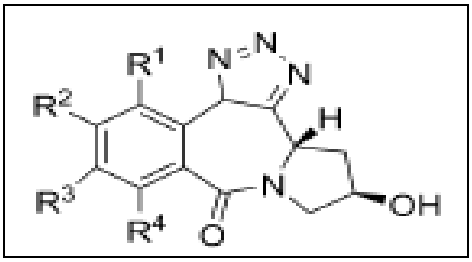


FIG. 4: SILYLATION AND DESILYLATION OF THYMIDINE ANALOG

Y. Saito *et al* reported the synthesis of carbocyclic and phosphonocarbocyclic analogues of ribavirin, an anti-HCV inhibitor. These compounds were evaluated to determine their spectrum of antiviral activity not only against HCV, but also against other important viruses. Some of the compounds displayed moderate IC_{50} against HIV-1 [65].

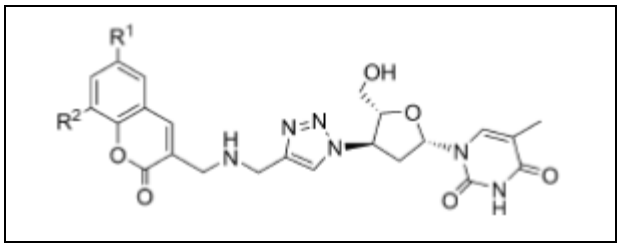


D. K. Mohapatra et al. explained a one-pot synthesis of novel tetracyclic scaffolds that incorporated a fusion of proline-1,2,3-triazole ring with [1,4]-benzodiazepin-(4H)-onering systems. All the derivatives were evaluated against protease inhibitors, and below depicted drug showed good serine protease inhibition activity [66].



T. O. Olomola *et al.* synthesized a series of 1,2,3-triazole-containing products by reaction of 3-alkynylmethylcoumarins with azidothymidine (AZT) in the presence of a CuI catalyst. Below mentioned structural skeleton was found to be potentialdual-action HIV-1 protease and non-

nucleoside reverse transcriptase inhibitors and as a scaffold for further structural study elaboration [67].



CONCLUSION: This review focuses on the diverse and potent antiviral activity profile of the 1,2,3 triazole derivatives. We have studied compounds of the past ten years to provide an outlook on the latest research developments on the scope of triazole derivatives as promising antiviral agents. This information may be useful to prospective researchers and medicinal chemists working in this arena to study this scaffold further. Researchers may exploit its biological potential appropriately and develop the pharmacologically significant antiviral agents of the future for treating various viral ailments.

ACKNOWLEDGEMENT: The authors would like to thank the institute for all the facility support.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

REFERENCES:

1. Lawrence CM, Menon S and Eilers BJ: Structural and functional studies of archaeal viruses. J Biol Chem 2009; 284(19): 12599-12603.
2. Koonin EV, Senkevich TG and Dolja VV: The ancient virus world and evolution of cells. Biol Direct 2006; 1: 29.
3. Edwards RA and Rohwer F: Viral metagenomics. Nat Rev Micro-biol 2005; 3(6): 504-510.
4. Canchaya C, Fournous G, Chibani-Chennoufi S, Dillmann ML and Brussow H: Phage as agents of lateral gene transfer. Curr Opin Microbiol 2003; 6(4): 417-424.
5. Breitbart M and Rohwer F: Here a virus, there a virus, everywhere the same virus. Trends Microbiol 2005; 13(6): 278-284.
6. Whitley RJ and Roizman B: Herpes simplex virusinfections. Lancet, 2001; 357(9267): 1513-1518.
7. Maddrey WC: Hepatitis B: an important public health issue. J Med Virol 2000; 61: 362–6.
8. Lee WM: Hepatitis B virus infection. N Engl J Med 1997; 337: 1733–45.
9. Lok AS, Heathcote EJ and Hoofnagle JH: Management of hepatitis B: 2000-Summary of a workshop. Gastroenterology 2001; 120: 1828–53.
10. Lok ASF and McMahon BJ: Chronic hepatitis B. Hepatology 2001; 34: 1225–41.
11. Giovanna Fattovich: Natural history of hepatitis B. Journal of Hepatology 2003; 39: 50–58.
12. Hirokazu Kimura: Ebola virus disease: a literature review, Journal of Coastal Life Medicine 2015; 3(2): 85-90.
13. "Global HIV & AIDS statistics — 2020 fact sheet". www.unaids.org. UNAIDS. Retrieved January 20, 2021.
14. "Fact Sheet - World AIDS Day 2019" (PDF). www.unaids.org. Archived (PDF) from the original on December 21, 2019. Retrieved December 21, 2019
15. Kallings LO: (March 2008). "The first postmodern pandemic: 25 years of HIV/AIDS". Journal of Internal Medicine. 263 (3): 218–43. doi:10.1111/j.1365-2796.2007.01910.x. PMID 18205765. S2CID 205339589.(subscription required)
16. Ahmad S, Hafeez A, Siddqui SA, Ahmad M and Mishra S: A Review of COVID-19 (Coronavirus Disease-2019) Diagnosis, Treatments and Prevention. EJMO 2020; 4(2): 116–125.
17. "COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)". ArcGIS. Johns Hopkins University. Retrieved 16 February 2021.
18. Kinchington D: Recent advances in antiviral therapy. J Clin Pathol 1999; 52(2): 89-94.
19. Kumar V, Sharma A and Sharma PC: Synthesis of some novel thiazolidinones from a long chain fatty acids as possible antiin- flammatory, analgesic and hydrogen peroxide scavenging agents. J. Enzyme Inhib. Med Chem 2010; DOI: 10.3109/14756366.2010. 489897 (Inpress).
20. Grimmett MR: Comprehensive Organic Chemistry. Ed 4th Per- gamon Press Oxford 1979; 357.
21. Gilchrist TL: Heterocyclic Chemistry. Ed 3rd Pearson Education India Singapore 2005; 298-307.
22. Thomas KD, Adhikari AV and Shetty NS: Eur J Med Chem 2010; 45: 3803–3810.
23. Ashok D, Chiranjeevi P, Kumar AV, Sarasija M, Krishna VS, Sriram D and Balasubramanian S: RSC. Adv 2018; 8: 16997–17007.
24. Li D, Mao T, Huang J and Zhu Q: Chem Commun 2017; 53: 1305–1308.
25. Dongamanti A, Aamate VK, Devulapally MG, Gundu S, Kotni MK, Manga V, Balasubramanian S and Ernala P: Bioorg Med Chem Lett 2015; 25: 898–903.
26. Speicher A: The Chemistry of Heterocycles: Structures, Reactions, Synthesis and Applications. 2nd Ed Wiley-VCH & Company Deutschland 2003; 200-211.
27. Shahar Yar, Mustaqeem Abdullah M, Husain AM, Bakht, MA and De Clercq E: Synthesis and evaluation of *in-vitro* antiviral activity of 2-[3-(substituted phenyl)-4,5-dihydro-1H-5-pyrazolyl] benzofuran-3-yl chloride derivatives. J Enzyme Inhib Med Chem 2009; 24(4): 949-956.
28. Maria de Lourdes GF, Pinheiro LC, Santos-Filho OA, Peçanha MD, Sacramento CQ and Machado V: Design, synthesis and antiviral activity of new 1H-1,2,3-triazole nucleoside ribavirin analogs. Medicinal Chemistry Research 2014; 23: 1501-1511.
29. KrajczykA,KulinskaK,KulinskiT, Hurst BL, Day CW and Smee DF: Antivirally active ribavirin analogues–4, 5-disubstituted 1,2,3-triazole nucleosides: Biological evaluation against certain respiratory viruses and computational modelling.Antiviral Chemistry and Chemotherapy 2014; 23: 161-171. DOI: 10.3851/IMP2564
30. Cheng H, Wan J, Lin MI, LiuY, Lu X and Liu J: Design, synthesis, and in vitro biological evaluation of 1 H- 1,2,3-triazole-4-carboxamide derivatives as new anti-influenza A agents targeting virusnucleoprotein. Journal of Medicinal Chemistry 2012; 55: 2144-2153. DOI: 10.1021/jm2013503

31. Piotrowska DG, Balzarini J and, Glowacka IE: Design, synthesis, antiviral and cytostatice valuation of novelisoxazolidinenucleotideanalogues with a 1,2,3-triazolelinker. Eur J Med Chem 2012; 47: 501-509.
32. He YW, Dong CZ, Zhao JY, MaL, Li YH and Aisa HA: 1,2,3-Triazole-containing derivatives of rupestonicacid: Click-chemical synthesis and antiviral activities against influenzaviruses. Eur J Med Chem DOI:10.1016/j.ejmech.2014.02.029.
33. Jordao AK, Afonso PP, Ferreira VF, De Souza MC, Almeida MC, Beltrame CO, Paiva DP, Wardell SM, Wardell JL, Tiekink ER, Damaso CR and Cunha AC: Antiviral evaluation of N-amino-1,2,3- triazoles against Cantagalo virus replication in cell culture. Eur J Med Chem 2009; 44: 3777–3783.
34. Wu J, Yu W, Fu L, He W, Wang Y, Chai B and Song C: Design, synthesis, and biological evaluation of new 20-deoxy-20- fluoro-40-triazole cytidine nucleosides as potent antiviral agents. Eur J Med Chem 2013; 63: 739-45.
35. Elia G, Belloli C and Cirone F: *In-vitro* efficacy of ribavirin against canine distemper virus. Antiviral Res 2008; 77(2): 108-113.
36. Robert G: Treating HCV with ribavirin analogues and ribavirin- like molecules. J Antimicrob Chemother 2006; 57(1): 8-13.
37. Sidwell RW, Bailey KW, Wong MH, Barnard DL and Smee DF: *In-vitro* and *in-vivo* influenza virus-inhibitory effects of vira- midine. Antiviral Res 2005; 68(1): 8-13.
38. Singh RJ and Singh DK: Synthesis, characterization and biological activity of some 1,2,4-triazole derivatives. E J Chem 2009; 6(3): 796-800.
39. Sharma PC, Sharma OP, Vasudeva N, Mishra DN and Singh SK: Anti-HIV substances of natural origin: An updated account. Nat Prod Rad 2006; 5(1): 70-78.
40. Jordao AK, Afonso PP, Ferreira VF, De Souza MC, Almeida MC, Beltrame CO, Paiva DP, Wardell SM, Wardell JL, Tiekink ER, Damaso CR and Cunha AC: Antiviral evaluation of N-amino-1,2,3-triazoles against Cantagalo virus rep- lication in cell culture. Eur. J. Med. Chem 2009; 44(9): 3777- 3783.
41. Zhu R, Wang M, Xia Y, Qu F, Neyts J and Peng L: Arylethynyltriazole acyclonucleosides inhibit hepatitis C virus rep- lication. Bioorg Med Chem Lett 2008; 18(11): 3321-3327.
42. Da Silva FDC, De Souza MCBV, Frugulhetti IIP, Castro HC, De Souza OSL, De Souza TML, Rodrigues DQ, Souza AMT, Abreu PA, Passamani F, Rodrigues CR and Fer- reira VF: Synthesis, HIV-RT inhibitory activity and SAR of 1- benzyl-1H-1,2,3-triazole derivatives of carbohydrates. Eur J Med Chem 2009; 44: 373-383.
43. Giffin MJ, Heaslet H, Brik A, Lin YC, Cauvi G, Wong CH, McRee DE, Elder JH, Stout CD and Torbett BE: A copper (I)-catalyzed 1,2,3-triazole azide-alkyne click compound is a potent inhibitor of a multidrug-resistant HIV-1 protease variant. J Med Chem 2008; 51: 6263-6270.
44. Perez-Castro I, Caamano O, Fernandez F, Garcıa MD, Lopez C and De Clercq E: Synthesis of 4-substituted-1,2,3-triazole carbanu- cleoside analogues of ribavirin *via* click chemistry. Org Biomol Chem 2007; 5: 3805-3813
45. Liu Y, Peng Y and Lu J: Design, synthesis and biological evaluation of new 1,2,3-triazolo-2′-deoxy-2′-fluoro- 4′-azido nucleoside derivatives as potent anti-HBV agents. Eur J Med Chem 2018; 143: 137–149.
46. Karypidou K, Ribone SR and Quevedo MA: Synthesis, biological evaluation and molecular modeling of a novel series of fused 1,2,3-triazoles as potential anti-coronavirus agents. Bioorg Med Chem Lett 2018; 28: 3472–3476.
47. Yan L, Yin Z, Niu L, Shao J, Chen H and Li X: Synthesis of pentacyclic iminosugars with constrained butterfly-like conformation and their HIV-RT inhibitory activity. Bioorg Med Chem Lett 2018; 28: 425–428.
48. Liu M, Xu Q and Guo S: Design, synthesis, and structure-activity relationships of novel imidazo[4,5-c]pyridine derivatives as potent non-nucleoside inhibitors of hepatitis C virus NS5B. Bioorg Med Chem 2018; 26: 2621–2631.
49. Kaoukabi H, Kabri Y and Curti C: Dihydropyrimidinone/1,2,3-triazole hybrid molecules: synthesis and anti-varicella-zoster virus (VZV) evaluation. Eur J Med Chem 2018; 155: 772–781.
50. Wu G, Zalloum WA and Meuser ME: Discovery of phenylalanine derivatives as potent HIV-1 capsid inhibitors from click chemistry-based compound library. Eur J Med Chem 2018; 158: 478–492.
51. Kaoukabi H, Kabri Y, Curti C, Taourirte M, Rodriguez-Ubis JC, Snoeck R, Andrei G, Vanelle P and Lazrek HB: Eur J Med Chem 2018; 155: 772–781.
52. Brik A, Alexandratos J, Lin YC, Elder JH, Olson AJ, Wlodawer A, Goodsell DS and Wong CH: Chem Bio Chem 2005; 6: 1167–1169.
53. Giffin MJ, Heaslet H, Brik A, Lin Y, Cauvi G, Mcree DE, Elder JH, Stout CD and Torbett BE: J Med Chem 2008; 6263–6270.
54. Y. Tian, Z. Liu, J. Liu, B. Huang, D. Kang, H. Zhang, E. De Clercq, D. Daelemans, C. Pannecouque, K. H. Lee, C. H. Chen, P. Zhan and X. Liu: Eur J Med Chem 2018; 151: 339–350.
55. G. Wu, W. A. Zalloum, M. E. Meuser, L. Jing, D. Kang, C. H. Chen, Y. Tian, F. Zhang, S. Cocklin, K. H. Lee, X. Liu and P. Zhan: Eur J Med Chem 2018; 158: 478–492.
56. I. Mohammed, I. R. Kummetha, G. Singh, N. Sharova, G. Lichinchi, J. Dang, M. Stevenson and T. M. Rana: J Med Chem 2016; 59: 7677–7682.
57. Hluhanich R, Kutty N, Liclican AC, McColl DJ, Squires NH and Lansdon ER: Triazole derivatives as non-nucleoside inhibitors of HIV-1 reverse transcriptase-Structure- activity relationships and crystallographic analysis. Bioorg Med Chem Lett 2008; 18: 1131–4.
58. Cheng ZY, Li WJ, He F, Zhou JM and Zhu XF: Synthesis and biological evaluation of 4-aryl-5-cyano-2H-1,2,3-triazoles as inhibitor of HER2 tyrosine kinase. Bioorg Med Chem 2007; 15: 1533-8.
59. Cao X, Wang W, Wang S and Bao L: Asymmetric synthesis of novel triazole derivatives and their in vitro antiviral activity and mechanism of action. European Journal of Medicinal Chemistry 2017; 139: 718–725. https://doi.org/10.1016/j.ejmech.2017.08.057
60. Mohammed I, Kummetha IR, Singh G, Sharova N, Lichinchi G, Dang J, Stevenson M and Rana TM: 1,2,3-Triazoles as amide bioisosteres: discovery of a new class of potent HIV-1 Vif antagonists 2016; J Med Chem 59(16): 7677–7682. https://doi.org/10.1021/acs.jmedchem.6b00247
61. Thakkar SS, Thakor P, Doshi H and Ray A: 1,2,4-Triazole and 1,3,4- oxadiazole analogues: synthesis, MO studies, in silico molecular docking studies, antimalarial as DHFR inhibitor and antimicrobial activities. Bioorg Med Chem 2017; 25(15): 4064–4075.
62. Guantai EM, Ncokazi K, Egan TJ, Gut J, Rosenthal PJ, Smith PJ and Chibale K: Design, synthesis and in vitro antimalarial evaluation of triazole-linked chalcone and dienone hybrid compounds. Bioorg Med Chem 2010); 18(23): 8243–8256.
63. Takhampunya R, Ubol S, Houng HS, Cameron CE and Padmanabhan R: Inhibition of dengue virus replication by

mycophenolic acid and ribavirin. J Gen Virol 2006; 87; 1947–1952.
64. Zhou GC, Weng Z, Shao X, Liu F, Nie X, Liu J, Wang D, Wang C and Guo K: Discovery and SAR studies of methionine-proline anilides as dengue virus NS2B-NS3 protease inhibitors. Bioorg Med Chem Lett 2013; 23: 6549–6554.
65. Vernekar SKV, Qiu L, Zhang J, Kankanala J, Li H, Geraghty RJ and Wang Z: 50 - Silylated 30 -1,2,3-triazolyl thymidine analogues as inhibitors of West Nile Virus and Dengue Virus. J Med Chem 2015; 58; 4016–4028.
66. Saito Y, Escuret V, Durantel D, Zoulim F and Schinazic RFLA: Agrofoglio Bioorg Med Chem 2003; 11: 3633 – 3639.
67. Mohapatra DK, Maity PK, Shabab M and Khan MI: Bioorg Med Chem Lett 2009; 19: 5241 – 5245.
68. Olomola TO, Klein R, Lobb KA, Sayed Y and Kaye PT: Tetrahedron Lett 2010; 51: 6325 – 6328.

How to cite this article:
Chopade PKD and Shaikh AR: Advancements and future perspectives of 1, 2, 3 triazole scaffold as promising antiviral agent in drug discovery. Int J Pharm Sci & Res 2022; 13(12): 4805-18. doi: 10.13040/IJPSR.0975-8232.13(12).4805-18.