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Antiviral and antiparasitic activities of various substituted triazole derivatives: A mini review

Mohammad Asif

Department of Pharmacy, GRD(PG) Institute of Management & Technology, 248009, Dehradun, (Uttarakhand), India
*Corresponding author's e-mail: aasif321@gmail.com

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The presence of three nitrogen hetero-atoms in five-membered ring systems defines an interesting class of compounds, the triazole. This may be of two types, the 1,2,3-triazoles and the 1,2,4-triazoles. Out of the two triazoles, 1,2,4-triazole have drawn great attention due to its wide variety of activities, low toxicities and good pharmacokinetic and pharmacodynamic profiles. Chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their effective biological activities such as anti inflammatory, analeptic, sedatives, antianxiety, antimicrobial, antimycotic and other pharmacological and chemical properties. In this article, antiviral and antiparasitic activities of triazole derivatives are discussed.

Capsule Summary: Antivral and antiparasitic activities of various substituted triazole derivatives were reviewed and it was found that triazoles, 1,2,4-triazole have drawn great attention, less toxic, have good pharmacokinetic as well as pharmacodynamic profiles and might be a potential antivral and antiparasitic candidate.

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INTRODUCTION

Triazole heterocyclic compounds have been paid special attention due to their potential applications as medicinal agents, agrochemicals, supramolecular ligands, biomimetic catalysts etc (Bai et al., 2007; Chang et al., 2011). Triazole ring is an important five-membered heterocycle with three nitrogen atoms, possesses aromaticity and is an electron rich system. This unique structure endows triazole derivatives to readily bind with a variety of enzymes and receptors in biological system and display a broad spectrum of biological activities (Mi et al., 2008; Mi et al., 2007; Wang and Zhou, 2011). Triazole compounds have showed great potential and been paid special attention. Furthermore, triazole ring can be used as an attractive linker to combine different pharmacophore fragments to produce innovative bifunctional drug molecules, providing a convenient and efficient pathway to develop various bioactive and functional molecules (Ouellette et al., 2011; Liu et al., 2011; Rodriguez-Fernandez et al., 2005). The triazole ring is also an important isostere of imidazole, oxazole, pyrazole, thiazole, amide moiety in designing various types of new drug molecules. Various triazole-based derivatives have been extensively prepared and investigated for their biological activities, which is one of the most active areas in the researches and developments of new drugs. Triazole derivatives, with pharmacological activity, less adverse effects, low toxicity, high bioavailability, good pharmacokinetics property, fewer multi-drug resistances and drug-targeting, diversity of drug administration, broad spectrum, better curative effect, have been frequently becoming clinical drugs or candidates for the treatment of various types of diseases. All these showed wide potential of triazole-based compounds as medicinal agents (Zhou et al., 2010; Zhou et al., 2009; Zhou et al., 2009). The researches and developments of the whole range

of triazole compounds as medicinal drugs from the reported as: antifungal, anticancer, antibacterial, antitubercular, antiviral, anti-inflammatory, analgesic, anticonvulsant, antiparasitic, antidiabetic, anti-obesitic, antihistaminic, anti-neuropathic, antihypertensive and so on (Hanane et al., 2010; Demirbas et al., 2004; Mathew et al., 2007; Prajapati et al., 2013; Hunashal and Satyanarayana, 2012; Singh, et al., 2010; Bozena and Jacek, 2004; Li, et al., 2007; Jordão, et al., 2011). Some comments on structure-activity relationships were also referred.

Triazoles as antiviral agents

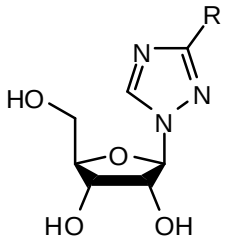
Viral infections are common disease with serious threat to human health. The traditional nucleosides are prominent drugs used for treatment of viral infections. However, the synthesis of modified nucleosides presents a major challenge due to their poor solubility in common organic solvents (Kumar and Malhotra, 2008). A large number of non-nucleoside compounds were investigated for their antiviral activities in recent decades. Triazole compound ribavirin (**1a**), one of the most representative antiviral drugs, is highly efficient agent against *Epatite C* and haemorragic fever (Mi et al., 2007) and is the only small-molecular-weight drug available so far for treating viral infections caused by *hepatitis C virus* (HCV) (Li et al., 2008). Inspired by the successful exploitation of ribavirin, more researchers devote to the exploitation of new triazoles as antiviral agents.

Nucleoside Triazoles as Antiviral Agents

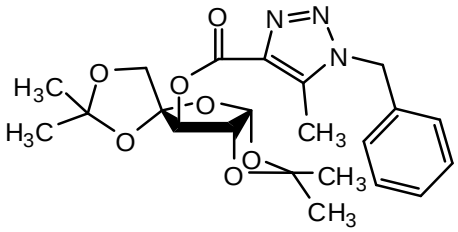
Nucleoside and nucleotide analogues have been critical parts for the treatment of human virus (Ray and Hostetler. 2011). Since nucleoside triazole antiviral drug ribavirin came out, researchers became aware of the antiviral potential of triazole compounds. Some triazoles have been developed as drugs or candidates for the treatment of different viral infections (Mi, et al., 2007). The modification of antiviral molecules with triazole moiety is a active topic (Chittepu et al., 2008). Phosphorylation of ribavirin into the mono and perhaps triphosphate forms were vital for its antiviral activity (Derudas et al., 2010). A series of phosphoramidate prodrugs of ribavirin were synthesized. Replacement of the amide group in ribavirin with an alkynyl group, which generated nucleoside triazole **1b**, could significantly reduce the replication of *dengue virus* serotype 2 (DENV-2) in cultured Vero cells and the effective concentration 50 (EC_{50}) of **1b** for DENV-2 was substantially lower than ribavirin. Moreover, compound **1b** reduced the replication of five additional flaviviruses, including DENV serotypes 1,3 and 4, *Langat virus* and *Modoc virus* (McDowell et al., 2010). Compound **1b** also showed EC_{50} values of 10 and 4.4 μmol/l for *Hantaan virus* (HTNV) and *Andes virus*, respectively (Chung et al., 2008). The research manifested that this compound represented a promising drug candidate for the treatment of flavivirus infections. Substitution of alkynyl moiety by other electron-withdrawing groups such as nitro or acetyl one decreased the antiviral efficacy sharply (Kumarapperuma et al., 2007). Several 1-benzyl-1*H*-1,2,3-triazoles attached to different carbohydrate templates were investigated for their anti-HIV activities. Compound **2** appeared to be the most active one that inhibited the HIV-1 reverse transcriptase catalytic activity with cytotoxicity higher than reference drug azidothymidine and Selective index (SI) higher than zalcitabine and didadosine (Da Silva et al., 2009). The significant activity, low cytotoxicity, and potential theoretical profile of this compound suggest that it may be considered as promising lead molecule for further synthetic and biological exploration. Acyclic nucleoside triazole 3, with an ethynyl moiety appended on the triazole nucleobase, could inhibit HCV subgenomic replication with an EC_{50} value of 22μg/mL and did not inhibit proliferation of the host cell at a concentration of 50μg/ml. The preliminary SAR study suggested that the appended phenyl ring as well as the rigid triple bond linker contributed importantly to the anti-HCV activity (Zhu et al., 2008). Meanwhile, the replacement aromatic ethynyl moiety with an aromatic hydrosulfide group could lead to the loss of antiviral activities (Liu et al., 2010).

Non-Nucleoside Triazole Compounds as Antiviral Agents

The development of non-nucleoside triazole compounds as antiviral agents has attracted much attention around the world due to their good antiviral activities (Seto et al., 2006; Di Grandi et al., 2010). The most famous one was peptide 1,2,3-triazole conjugate HNG-150 (**4**), which exhibited a sub-micromolar affinity to gp120 and showed broad spectrum inhibition of the molecular interactions of CD4 with gp120s derived from viruses. In addition, HNG-105 inhibited infection of recombinant luciferase containing viruses pseudotyped with envelopes (Gopi et al., 2009; Umashankara et al., 2010). Meanwhile, a literature reported that the replacement of benzene ring with a metallocene moiety would result in the reduction of its off-rate and enhancement of its affinity and antiviral potency (Cocklin et al., 2007). The potency of compound **4** makes it a promising viral envelope inhibitor lead for developing anti-HIV-1 treatments. Given the ubiquitous nature of the peptide linkage in biological molecules, the replacement of amide bond with isosteres in potential drug candidates has been a continual goal to develop new bioactive compounds. A successful example is the substitution of peptide moiety by a 1,2,3-triazole ring. A novel compound **5**, synthesized by the incorporation of a 1,2,3-triazole ring instead of the amide group into antiviral drug amprenavir, exhibits quite strong inhibitory activity against normal or mutative HIV-1 protease, and is currently in clinical trial (Brik et



1a R=$CONH_2$ Ribavirin



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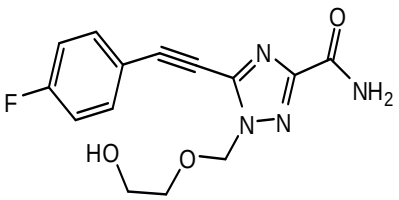

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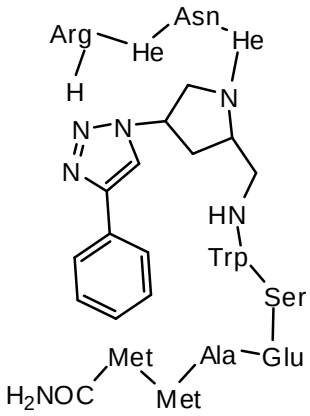
1b R= $-C\equiv CH$



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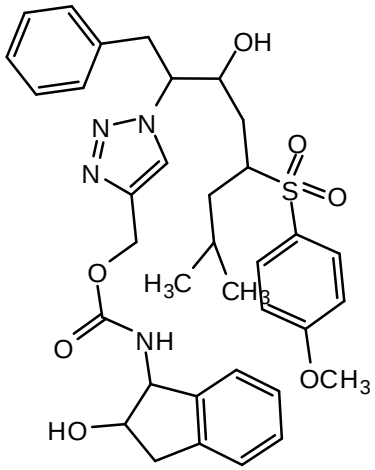

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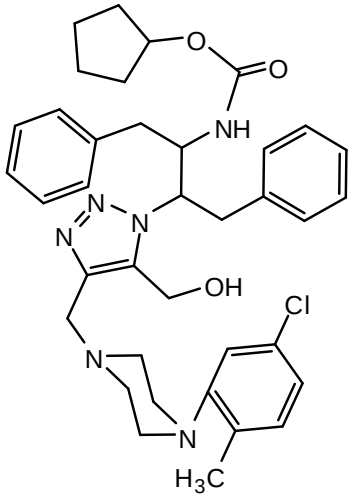

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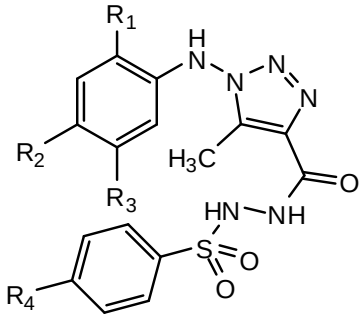
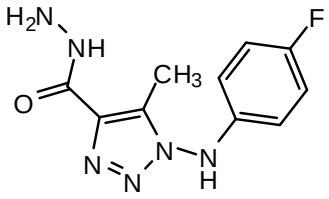


7a, R_1= H, R_2= F, R_3= H, R_4= Me

7b, R_1= Cl, R_2= H, R_3= Cl, R_4= H



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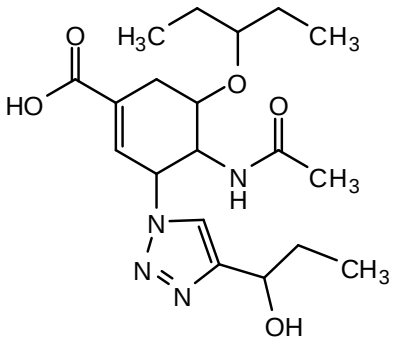

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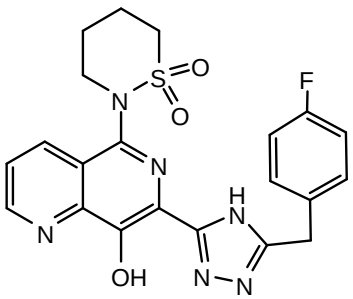

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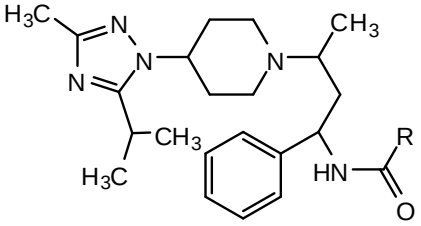
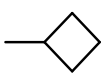
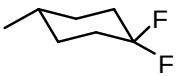
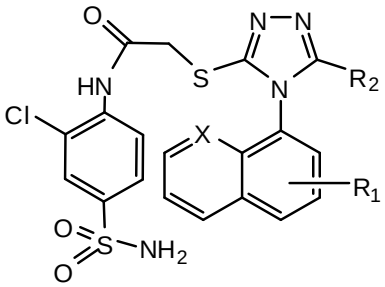


11aR=



11b R=





12 R1=4-CH_3, 2,4-CH_3

R_2 = CH_3, CF_3 X=N, CH

al., 2005; Giffin et al., 2008). Additionally, 1,2,3-triazole ring is also widely applied in antiviral field as the isostere of other groups (Li et al., 2006; Weiwer et al., 2009), which shows the potential of 1,2,3-triazole ring as antiviral pharmacophore.

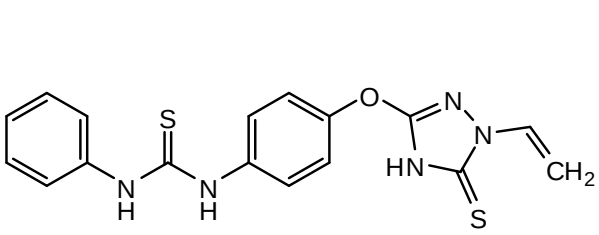
Triazole compound **6**, a substituted product of amide moiety in compound **5** by a piperizine group, was reported to be HIV-1 protease inhibitor with Ki value as low as 0.008 μmol/l. However, the replacement of triazole ring with a range of alternative linkers led to greatly reducing protease inhibition (Whiting et al., 2006), which revealed that triazole ring was essential for the antiviral activity rather than a simple connector.

Herpes simplex viruses 1 (HSV-1) is a class of DNA viruses, which causes recurrent infections such as gingivostomatitis, herpes labialis, herpes keratitis *etc*. (Jordão et al., 2011). Some triazole compounds have good biological activities against this kind of viruses. Arysulfonylhydrazine 1,2,3-triazoles **7a-b** displayed potent activity against HSV-1 with IC_{50} values of 1.30 and 1.26 μmol/l. The compounds **7a** and **7b** could be considered as promising candidates for the development of new derivatives with anti-HSV-1 activity. In addition, a lot of amino, hydrosulfo (Zhang et al., 2007; El-Sabbagh and Rady, 2009) or hydrazine substituted triazoles also showed good antiviral ability. Compound **8**, a novel *N*-amino-1,2,3-triazole derivative, exhibited a significant antiviral effect on *Cantagalo virus* replication by more than 55% at 50 μmol/l (Jordão, et al., 2009). A new series of triazole-containing carbocycles related to oseltamivir showed that compound **9** was an effective group-1 neuraminidase inhibitor against virus-like particles (VLPs) containing an influenza virus N1 activity (Mohan et al., 2010), which provided lead structure for further optimization. 1,2,4-Triazole compound **10**, with a sulfamide-containing naphthyridine moiety, displayed significant bioactivity against HIV-1 integrase with IC_{50} value of 0.011 μg/mL and therapeutic index (CC50/EC50) above 104 (Johns et al., **2009)**. Recently, a series of 4-piperidinyltriazoles as potent anti-HIV agents, compounds **11a** (Barber et al., 2009) and **11b** (Barber et al., 2009) were identified as the most active ones, which showed good whole cell antiviral activity. Compound **11a** also had excellent selectivity over the human ether-a-go-go related gene (hERG) ion channel with complete oral absorption. Triazole **12** gave potent antiviral activities against efavirenz- and nevirapine-resistant viruses containing K103N and/or Y181C mutations or Y188L mutation (De La Rosa et al., 2006). Triazole-3-thione **13** showed moderate protection against *Coxsackie virus* B4 with an MIC value of 16 μg/ml (MIC value of drug acyclovir was higher than 400 μg/mL) and a selectivity index of 5. This triazole was also active against thymidine kinase positive *Varicella-zoster virus* (TK+ VZV) with an EC50 value of 9.9 μg/mL (EC50 of acyclovir was 0.17μg/ml) (Kucukguzel et al., 2008). A sulphanyltriazole (**14**) as an HIV-1 non-nucleoside reverse transcriptase inhibitor via high through put screening (HTS) cell-based assay. Chemical modifications and molecular modeling studies were carried out to establish its SAR and to understand its interactions with the enzyme. These modifications led to the identification of sulphanyl triazoles with low nanomolar potency for inhibiting HIV-1 replication and promising activities against selected NNRTI resistant mutants. These potent sulphanyl triazoles could serve as advanced leads for further optimization (Wang et al., 2006). A series of 1,2,4-triazoles (**15**) tested against several NNRTI-resistant HIV-1 isolates. Several of these compounds exhibited potent antiviral activities against efavirenz- and nevirapineresistant viruses, containing K103N and/or Y181C mutations or Y188L mutation (De La Rosa et al., 2006). A N-amino-1,2,3-triazole derivatives, 1-(substituted phenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid ethyl esters, and 1-(4-substituted-phenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid hydrazides on Cantagalo virus replication. 1-(4-Fluoro-phenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carboxylic acid hydrazide (**16**) exhibited significant antiviral effect (Jordao et al., 2009).

The HIV (retrovirus) is a virus resulting in the slow depletion of immune system of the affected human beings resulting in opportunistic infections. Some compounds were evaluated for the anti-HIV activity. The 4-[(1,2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-*N*(4,6-dimethy l-2- pyrimidinyl)-benzene sulphonamide and its derivatives (**17)** were found active against replication of HIV-1 and HIV-2 in MT-4 cells (Kucukguzel and Tatar, 2008). Various derivatives of trisubstituted triazoles (**18)** were prepared as inhibitors of reverse transcriptase and the two derivatives with difference in thio group position were found out to be most active compounds (Jordao and Afonso, 2009). The thiourea derivatives obtained from 5-[(4-amino phenoxy) methyl]-4-alkyl/aryl-2, 4-dihydro-3H-1,2,4-triazole-3-thiones (**19**) which proved to be having a good activity against cox sacie virus B4, also active against the thymidine kinase positive *Varicella zoster* Virus (Saini and Dwivedi, 2013). Compound (**20**) N-amino-1,2,3-triazole and evaluated for Antiviral activity against cantalago virus (Amin and Islam, 2006).

The ethyl1-(7-phenyl-2H-3,5,6,7-tetrahydro-imidazo [2, 1-c] [1,2,4]triazol-3-yl)formate (**21**) The influence of the ethyl 1-(7-phenyl-2H-3,5,6,7-tetrahydro-imidazo[2,1-c][1,2,4]triazol-3-yl) formate on human adenovirus-5 (Ad-5) and human enterovirus (Echo-9) replication has been investigated. For this compound, the activity against the selected DNA (Ad-5) and RNA (Echo-9) viruses and the cytotoxicity towards normal GMK (Green Monkey Kidney) cells were determined. Ethyl-1-(7-phenyl-2H-3,5,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazol-3-yl)formate (Mujagic et al., 1983). Antiviral activity has been shown in D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (**22**) (Streeter et al.,1973). The 1-[(1,5-Dialkyl)-1H-1,2,4-triazol-3-yl)methyl] thymines (**23**) and evaluated their antiviral activity (Al-Soud and Al-Masoudi, 1999).

Triazoles as antiparasitic agents



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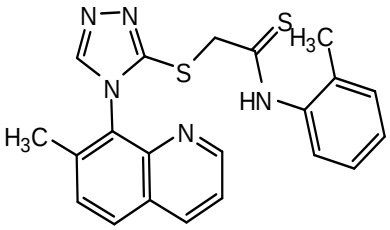

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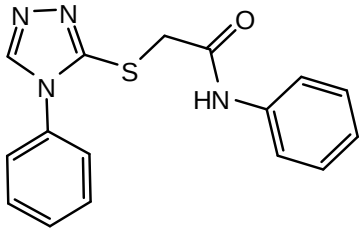

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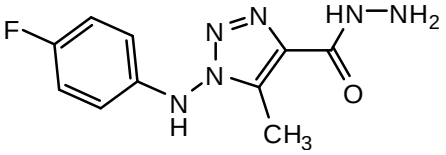

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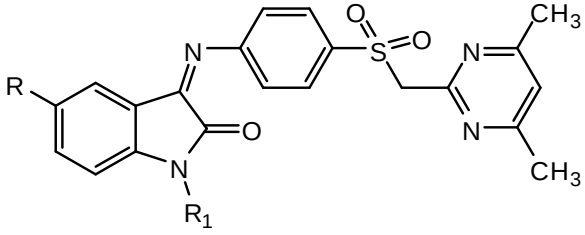

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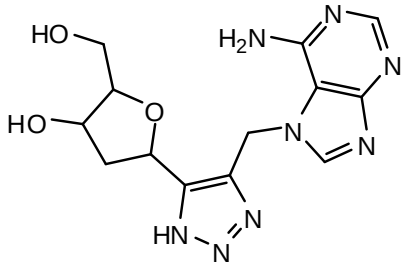

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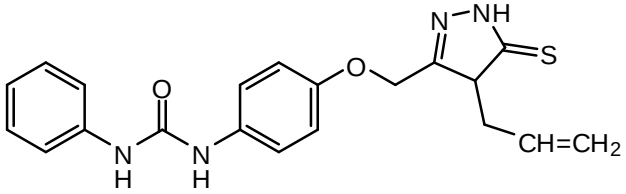

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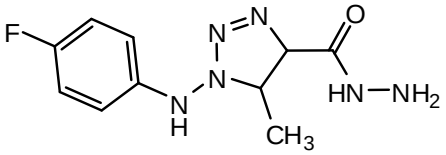

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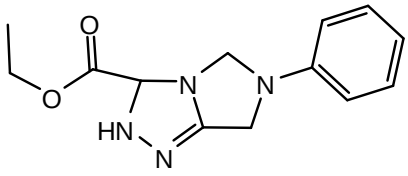

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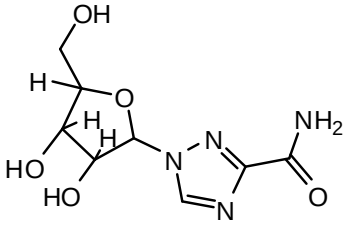

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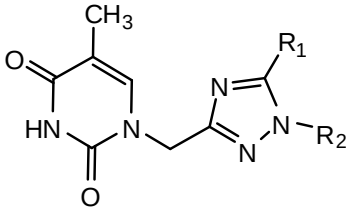
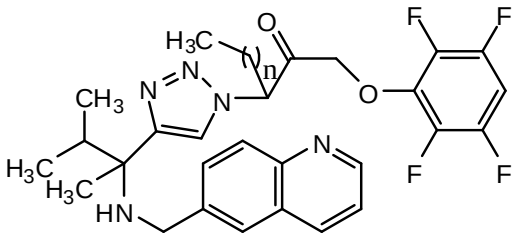


23 R_1=CH_3, $(CH_2)_6$ R_2=CH_3, -$(CH_2)_6$

Tropical diseases caused by protozoan parasites like trypanosomiasis, leishmaniasis, and malaria and such diseases cause the death of about two million people per year (Pagliero et al., 2010). Old and ineffective therapeutic agents like nitrofurans and nitroimidazoles are unsatisfactory due to frequent toxic side effects and limit efficacy in the chronic form of the disease (Tempone et al., 2007). The urgent need for the discovery of safe and effective new drugs against these protozoan infections is obvious. Various nitroimidazole drugs, triazole compounds act as antiparasitic agents (Corrales et al., 2011; Hans et al., 2010). Chagas' disease, caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*), is a neglected disease that affects a lot of people in areas of endemicity in Latin America (Maldonado et al., 2010). There is considerable interest in the development of new drugs for the treatment of Chagas' disease due to the limited efficacy, particularly in the prevalent chronic stage, and frequent deleterious side effects of the clinical drugs (Carvalho et al., 2010; Da Silva Júnior et al., 2010). A work showed that triazole antifungal drug posaconazole in combination with amiodarone which was most frequently used to treat arrhythmias, displayed significant anti-*T. cruzi* activity. The amiodarone, in addition to disrupting the parasites' Ca^{2+} homeostasis, also blocked



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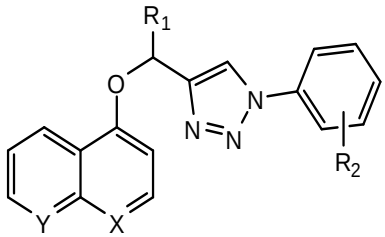
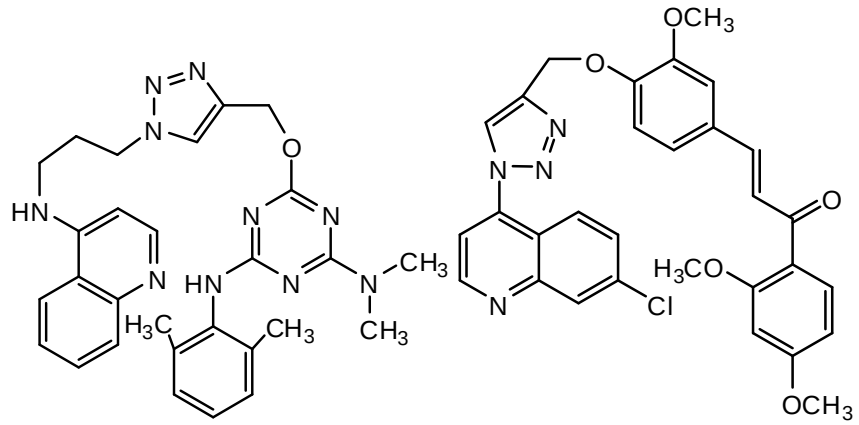
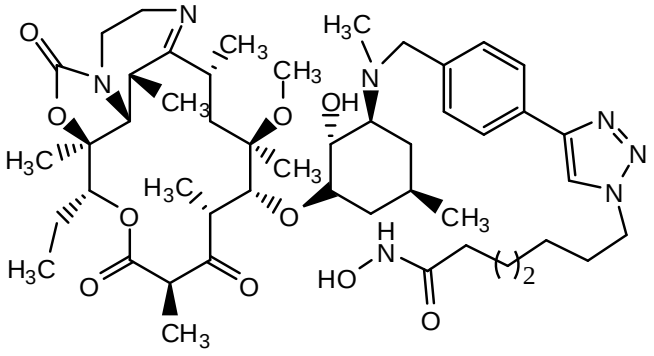


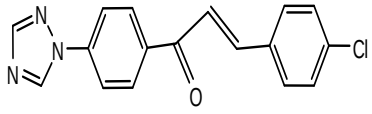
25a, R_1=(S)CH_3, R_2= 3,4-Cl, X=N^+O^-, Y=CH
25b, R_1=(R)CH_3, R_2= 4-Cl, X=CH, Y=N^+O^-



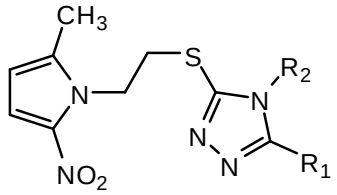
26 **27**



28



29



30a, R_1=Ph, R_2=3-pyridine
30b, R_1= 4-OCH_3Ph, R_2=4-pyridine
30c, R_1=1-naphthalene, R_2=4-pyridine

ergosterol biosynthesis and posaconazole affected Ca^{2+} homeostasis (Benaim et al., 2006). The possibility of novel combination therapy approaches to treat Chagas' disease using currently approved drugs.

It has been confirmed that *T. cruzi* infection could be cured in cell, mouse, and dog models by treatment with irreversible inhibitors of cruzain (Barr et al., 2005). Triazole compound **24** regarded as a promising drug for Chagas' disease (Brak et al., 2008; Baskin-Bey et al., 2007). The initial evaluation of inhibitor **24** in a mouse model of Chagas' disease showed that visible signs of Chagas disease such as abdominal swelling, malaise, and weakness of the hind legs were not observed for the treated mice and also well tolerated with no apparent signs of toxicity (Brak et al., 2010). Compounds **25a-b** represented a promising drug lead for the treatment of Chagas' disease. Selective inhibition of *C. parvum* Inosine 5'-Monophosphate Dehydrogenase (*Cp*IMPDH) is an attractive for the specific inhibition of parasites (Gargala, 2008). Triazole compounds **25a-b** showed noticeable *Cp*IMPDH inhibitory activity. Various electron-withdrawing groups in the 3- and/or 4-positions, but not the 2-position, of the pendent phenyl ring increased in *Cp*IMPDH inhibitory activity. The small alkyl group (methyl) was required on the R_1-position of the ether with the (R)-enantiomers demonstrating significantly more activity than the (S)-enantiomers (Maurya et al., 2009). These 1,2,3-triazole *Cp*IMPDH inhibitors can serve as potential lead compounds for the therapeutic development of cryptosporidiosis. Malaria remains one of the most widespread infectious diseases, and poses a great challenge due to the spread of drug-resistant *Plasmodium falciparum* strains. Many efforts have been devoted to the synthesis of structurally novel compounds with potential antimalarial activity. Some compounds with combination of triazole ring into quinoline moiety could produce high bioactive compounds. Triazole-containing chloroquinoline derivative **26** and its analogues showed promising antimalarial activity against D6 and W2 strains of *P. falciparum* without toxicity against Vero cells (Manohar et al., 2011). Several chalcone-chloroquinoline hybrids were found to be notably active, and the most active compound

27 exhibited the submicromolar IC_{50} values against the D10, Dd2 and W2 strains of *P. falciparum* (Guantai et al., 2010).

Macrocyclic depsipeptides, a class of excellent anticancer agents possess the most complex cap groups, and demonstrate excellent HDAC inhibition potency and isoform selectivity. Interestingly, the incorporation of 1,2,3-triazole ring into the macrocycle to replace the peptide moiety, which afforded triazole derivative **28**, showed the most potent antimalarial activity, which was between 2- to 4-fold more potent than the control compound SAHA. Moreover, triazole macrocycle **28** was several-fold more selectively toxic to *P. falciparum* (D6 clone) and *P. falciparum* (W2 clone) compared to SAHA. This result also confirmed that this compound partly derived their antimalarial activity through intracellular inhibition of pf-HDAC1 activity (Mwakwari et al., 2010). There are also some other HDAC inhibitors possessing excellent antimalarial and antileishmanial activities (Patil et al., 2010), which prognosticate that these HDAC inhibitors would be developed as an important class of antimalarial drugs. The antiplasmodial evaluation for a series of 1,3-diaryl propenone derivatives showed that 1,2,4-triazole substituted chalcone **29** was the most effective compound in inhibiting the growth of *P. falciparum in vitro* with IC_{50} value of 1.52 µg/ml. Substitution of triazole ring with a benzotriazole group decreased the bioactivity sharply. This indicated that in triazole substituted derivative, spacing of nitrogen and the orientation of the molecule on active site of enzyme might be good enough to provide stronger and effective hydrogen bonding with His 67 of cysteine protease (Mishra et al., 2008). Triazoles **30a-c** were prepared by the introduction of a triazole ring into antiparasitic drug metronidazole and gave strong antiparasitic activities against *Entamoeba histolytica* and *Giardia intestinalis*. Compound **30a** showed the strongest activity against *G. intestinalis*, with IC_{50} value of 0.76µmol/L, which was more active than metronidazole itself. The IC_{50} values of compounds **30b** (0.48 µmol/L) and **30c** (0.79 µmol/l) against *E. histolytica* were also much smaller than those of metronidazole (5.03 µmol/l) (Saadeh et al., 2010).

DISCUSSION

Triazoles are the class of heterocyclic compounds 1 which are under study since many a years. Triazole is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms azole ring are readily able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions, and thus display versatile biological activities (Ragenovic et al., 2001; Kartritzky, 1985; Varvarason et al., 2000; Gokce et al., 2001; Pintilie et al., 2007; Zan et al., 2002; Chem et al., 2000). In recent years, the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. Pyrimidines, D-manno-pentitol-1-yl-1,2,4- triazoles, benzotriazoles, indoles, quinolones, triazolo thymidines, are in record (Al-Soud and Al-Masoudi, 1999; Al-Soud et al., 2003; Al-Soud and Al-Masoudi, 2003). Literature survey reveals that triazole derivatives exhibited wide range of biological activities including antibacterial, antifungal, antitumour, anti-inflammatory, antitubercular, anti-convulsant, anticancer, antimalarial, antiviral, analgesic, antimigrain etc (Chun et al., 2004; Jubie et al., 2010; Sztanke et al., 2008; Mevlut et al., 2007; Haythem et al., 2010; Rao et al., 2000). This has been noticed so far, that modifications on triazole moiety results in the formation of compounds with valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. Thus many more modifications on triazole moiety can be possible and needs to be continued for the use of mankind.

CONCLUSION

Triazole has unique moiety that is responsible for various biological activities. This article highlighted research work of many researchers reported in literature for different pharmacological activities on synthesized triazole compounds. This review has presented comprehensive details of triazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of triazole for many diseases whose treatment are difficult in the medical sciences.

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