Asian Journal of Chemistry; Vol. 33, No. 11 (2021), 2599-2607

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.23443

REVIEW

Recent Advances in Tetrazole Derivatives as Potential Antiviral Agents

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Received: 28 July 2021; *Accepted*: 28 September 2021; *Published online*: 20 October 2021; AJC-20536

Viruses use the host cell's biochemical machinery for replication and survival; and also undergo mutations to evade the immune response and achieve better transmission. These features make it challenging to develop selective drugs to kill viruses only and not the host cells. New and effective pharmaceutical agents are required to overcome this challenge. Tetrazole moiety, as a bio-isostere of carboxylic acid/amide group, has been extensively used as a potent pharmacophore in several bioactivities. Intrigued by the necessity of finding new antiviral compounds and tendency of tetrazole scaffolds to render various bioactivity profiles, this review article comprising literature reports of tetrazole-based synthetic compounds with promising antiviral activity is presented. This review comprises significant literature reports from the scientific databases published during the past four decades. It is found that tetrazole based molecules are promising endeavor for the development of potential agents against influenza virus, HIV, HCV and other viruses.

Keywords: Tetrazole, Antiviral, Bio-isostere, HIV, Influenza, Tetrazole derivative.

INTRODUCTION

Viruses, unlike other pathogens such as bacteria or fungi, cannot live and reproduce on their own and necessarily need a host cell for survival and replication. After infecting a cell, the virus uses all the necessary biochemical machinery of the host for replication of the viral genome and its further spread to the other host cells. The fact that it is difficult to kill the infecting viruses without killing the host cells makes it challenging to develop medicines against viruses. Keeping this in view, there is a constant need for new and improved pharmacotherapy regimens against viruses to prevent and treat a number of significant conditions inadequately controlled at present [1]. Antiviral agents usually are designed to disable viral proteins or block the viral replication process. Researchers are always in a quest to find the best combination of pharmacophores to develop new bioactive compounds. One such pharmacophore is tetrazole and molecular scaffolds based on tetrazoles are known for possessing a wide range of significant therapeutic benefits attributable to their isosteric character to carboxylic acid and *cis/trans*-amide moieties, metabolic stability and beneficial physico-chemical properties [2-4]. This review emphasizes contemporary strategies used for the inclusion of tetrazole moiety in the development of high-efficacy tetrazole-based antiviral therapeutic agents.

Structural characteristics of tetrazole: Tetrazole is a nitrogen-containing aromatic heterocycle comprising one carbon and four nitrogen atoms. This doubly unsaturated five-membered aromatic ring is not found in the nature. However, there are umpteen synthetic strategies available in the literature. Tetrazoles can be classified into un-, mono- and disubstituted tetrazoles depending on the number of substitutions present. Tetrazoles have the highest nitrogen content among the stable heterocycles.

Tetrazole is a metabolically stable, promising pharmacophore which acts as a bio-isosteric analogue for carboxylic acid and *cis/trans*-amide functional groups [5-8]. Tetrazole moiety has been reported as a bio isostere of carboxylic acid substituents due to the similarities in hydrogen bond environment around both the moieties and their corresponding anions [9]. Additionally, the annular tautomerism exhibited by tetrazole and its derivatives, as well as the conformational flexibility of the tetrazole-based scaffolds, puts them forward as an interesting family of molecules to be investigated from medicinal chemistry perspective [10].

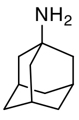
All these properties put forward the use of tetrazoles, in combination with other pharmacophores, as isosteric substituents of crucial functional groups in the development of biologically active substances.

Biotransformation of tetrazole: Bio-isosterism is a valuable and rational strategy for lead modification and drug design prevailing in medicinal chemistry that focuses on altering unfavourable ADME (absorption, distribution, metabolism and excretion) properties of a drug molecule. In case of tetrazole, a prolonged half-life is observed because of the enhanced metabolic stability of the tetrazole moiety. Additionally, tetrazole moiety is metabolically stable to biological transformation and degradation pathways, occurring in the liver, affecting the carboxylic acid functional group [11]. According to the literature, tetrazoles are resistant to major biological metabolic degradation pathways, like amino acid conjugation or β-oxidation. Better performance of tetrazole-based drugs is attributable to the possible better membrane penetration resulting from increased lipophilicity. Furthermore, the high density of nitrogen in tetrazoles favours more hydrogen bond formation or π-stacking with the receptor recognition sites, leading to an increased binding affinity with the target receptors [12].

In this review, the present literature is surveyed for studies indexed in PubMed, Google Scholar, EMBASE, PLOS ONE, Europe PMC and ScienceDirect databases. Only those articles published between 1978 and 2021 were included in this review. The titles, abstracts and full texts of relevant studies available online with due credit to the sources were included. The keywords, tetrazole, tetrazolyl, pharmacological activity, antiviral, anti-influenza, anti-HIV, anti-HCV, anti-HSV, anti-TMV, anti-picornavirus, human immunodeficiency virus, hepatitis C virus, tobacco mosaic virus, SARS-CoV-2, both individually and in combination were applied in the survey and then scrutinized all the relevant articles for their purpose of the study and findings. Articles whose main findings focus on the tetrazole based heterocyclic compounds as antiviral agents were included in the present study.

The use of antiviral vaccines and drugs is the major pharmacotherapeutic intervention regime to control viral infections by alleviating the symptoms and shortening the viral infection duration. There is substantial literature available on the use of tetrazole moiety in combination with other pharmacophores in the discovery of various antiviral agents. Tetrazolyl pharmacophore has been employed effectively in: (i) modification of active natural substances like peptides, terpenes and nucleosides; and (ii) synthesis of hybrid molecules while combining tetrazole moiety with other bioactive pharmacophores like indole ring and adamantane ring, to increase the effectiveness of the already existing therapeutic agents. This review describes most of the new and modified tetrazole-based antiviral agents found useful against different types of virus-born ailments.

Activity against influenza virus: Influenza viruses are responsible for seasonal and sporadic respiratory infections in humans. The recent emergence of multidrug-resistant influenza viruses has caused concern among healthcare providers, as available vaccines and small molecule drugs are offering insufficient responses against influenza. The M2 channel blockers amantadine (**1**) and rimantadine (**2**) are FDA-approved small molecule drugs used for the treatment of influenza A infections [13]. The adamantane nucleus present in both of these drugs inspired Seliverstova *et al.* [14] to synthesize and evaluate 2-adamantyl-5-aryl-2*H*-tetrazole (**3a-d**) for their anti-influenza activity against A/Puerto Rico/8/34 (H1N1) virus strains. These compounds, although showed high viral inhibition, were found potentially cytotoxic as well and suggested that these compounds may be used as a basic framework for further research. A similar strategy was followed by Mykolaichuko *et al.* [15] to synthesize compounds, where amino group of existing active molecules was replaced with a polynitrogenous heterocyclic fragment *i.e.* tetrazole. A series of 2-adamantyl-5-aryl-2*H*-tetrazole was synthesized and evaluated against influenza A/Puerto Rico/8/34 (H1N1) virus strain. Out of the total compounds synthesized (**4a-d**), three compounds showed moderate inhibitory activities but high cytotoxic activities. The tetrazole derivative 2-[2-(adamantan-1-yl)-2*H*-tetrazol-5-yl]-6-bromo-4-nitroaniline (**4d**), containing an amino group and a bromine atom turned out to be the least toxic to cells (IC$_{50}$ = 167 μg/mL) in combination with moderate activity against virus (IC$_{50}$ = 15 μg/mL). Recently, Garaev *et al.* [16] reported that a series of compounds obtained by reacting aminoadamantans with amino acids and other organic molecules utilizing classical peptide synthesis methods, which show a considerable anti-influenza activity (IC$_{50}$ = 0.5 to 2.5 μM) against influenza virus A/California/07/2009 (H1N1) strain.



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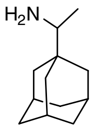

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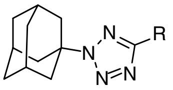
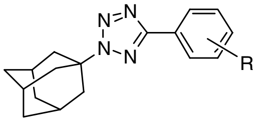
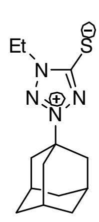


3a R=Ph
3b R=2-MeC$_6$H$_4$
3c R=pyridin-4-yl
3d R=4-ClC$_6$H$_4$



4a R=4-I
4b R=4-Cl
4c R=3-Cl, 4-NH$_2$
4d R=2-NH$_2$, 3-Br, 5-NO$_2$

In search of new potent antiviral compounds against influenza with a broad spectrum of activity, Zarubaev *et al.* [17] also synthesized and evaluated a set of di-, tri- and tetrazole derivatives of adamantane for their anti-influenza activities against rimantadine-resistant influenza virus strain A/Puerto Rico/8/34. Some of the synthesized azolo-adamantanes (**5-11**) possess better antiviral and lesser cytotoxic activity compared to rimantadine. Recently, Popova *et al.* [18] synthesized a few tetrazole-thymidine hybrid compounds which have shown moderate *in vitro* antiviral activity with low cytotoxic activity. The following tetrazole derivatives showed moderate anti-influenza activities when evaluated against influenza virus A/Puerto Rico/8/34 (H1N1) strain: 3′-(4-(1*H*-tetrazol-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)thymidine (**12**), (IC$_{50}$ = 39.6 μg/mL), 3′-(4-(2*H*-5-ethoxycarbonyltetrazol-2-ylmethyl)-1*H*-1,2,3-triazol-1-yl)thymidine (**13a**), (IC$_{50}$ = 31.6 μg/mL) and 3′-(4-(2*H*-5-(4-nitrophenyl)-tetrazol-2-ylmethyl)-1*H*-1,2,3-triazol-1-yl)thymidine (**13b**), (IC$_{50}$ = 46.4 μg/mL). These hybride tetrazole derivatives showed moderate anti-influenza activities when evaluated against influenza virus A/Puerto Rico/8/34 (H1N1) strain. Zorina *et al.* [19] in 2017 reported the synthesis and antiviral activity evaluation of tetrazole hybrids with natu-



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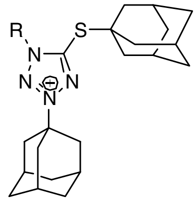
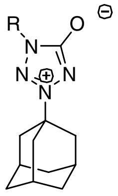
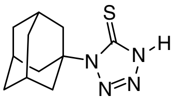


6a R=Et
6b R=4-(CH$_3$OOC)C$_6$H$_4$



7a R=Et
7b R=4-(CH$_3$OOC)C$_6$H$_4$



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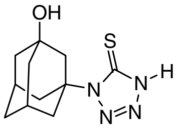

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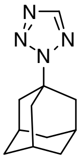

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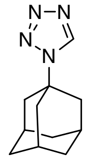

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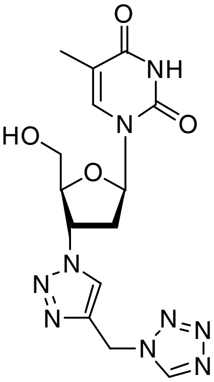
rally occurring dammarane triterpenoids for their antiviral activity. This combination was aimed to improve the pharmacological profile and reduce the side effects of already existing molecules. Out of the 17 synthesized compounds, four compounds showed considerable activity. The highest antiviral activity was observed in dammarane derivative 20(S)-3-(2-1*H*-tetrazol-5-ylethoxy-imino)-25,26,27-trinor-20,24-olidedammarane (**14**).

An *in silico* study done by Watanabe *et al.* [20] reported a quinolinone derivative bearing a tetrazole moiety as a potent anti-influenza compound. This compound designated as PA-49, which was found to inhibit the replication of influenza virus A/WSN/33 with an IC$_{50}$ value of 0.47 µM. Docking studies revealed that PA-49 might be useful against many viruses as it interrupts the PA–PB1 interface (the place where important amino acids are conserved in most of the virus strains). Non-annulated tetrazolylpyrimidines, binuclear heterocyclic derivatives of tetrazole and pyrimidine, have been recently reported to possess anti-influenza properties [21]. The synthesized compounds containing different linker groups like a sulfur atom, methylene, pyrazolyl and hydrazinylcarbonylmethyl groups were used to connect tetrazole and pyrimidine heterocycles. Among the synthesized compounds, 5-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]-1*H*-tetrazol-1-yl acetic acid (**15**) was found to be a promising compound as it has moderate antiviral activity with low cytotoxicity and double the selectivity index compared to the reference drug rimantadine.

In an extensive study reported by Zhang *et al.* [22], several multi-component Ugi-azide reaction products were synthesized as antiviral drug candidates, followed by docking studies to screen a small molecule library comprising inhibitors that target the influenza polymerase PA$_C$-PB1$_N$ interactions. These bunch of compounds was evaluated for their antiviral activity through an antiviral plaque assay to obtain a tetrazole compound **16**, which showed a broad-spectrum antiviral activity. Subsequent structure-activity relationship studies led to the discovery of 1{1-[(S){1-[(1S)-1-phenylethyl]-1*H*-1,2,3,4-tetrazol-5-yl}(thiophen-3-yl)methyl]piperidin-4-yl}-2,3-dihydro-1*H*-1,3-benzodiazol-2-one (**17**) with an improved selectivity index and genetic barrier to oseltamivir drug resistance.

A few early attempts are reported in this field. In 1985, Hutchison & Naylor [23] synthesized some tetrazole phosphonic acid compounds and evaluated for their antiviral activities.



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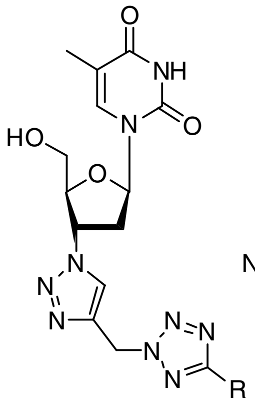
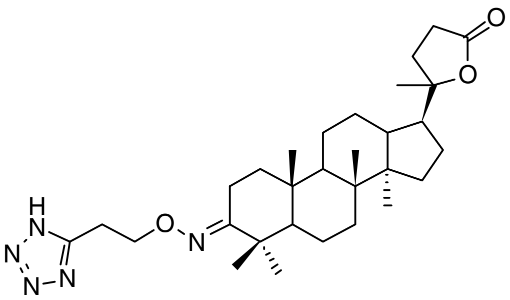


13a, R=COOC$_2$H$_5$
13b, R=*p*-NO2-Ph



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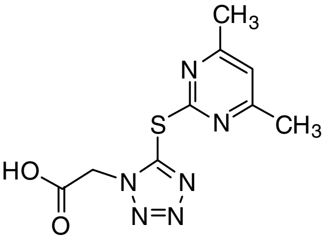

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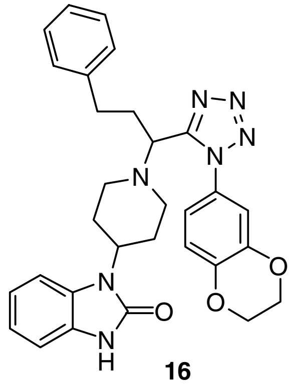

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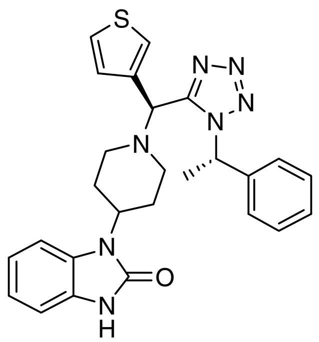

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Out of these compounds, 5-(phosphonomethyl)-1*H*-tetrazole and 5-(thiophosphonomethyl)-1*H*-tetrazole were found to inhibit the influenza virus transcriptase; however, these activities were not considered significant. Much earlier, in 1976, Poonian *et al.* [24] synthesized tetrazole ribonucleosides for the first time and evaluated them as antiviral agents. Antiviral testing of these synthetic tetrazole nucleosides was performed against influenza A2/Asian/J-305 virus infection in mice.

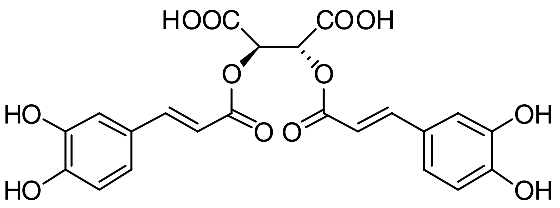
Activity against human immunodeficiency virus (HIV): Human immunodeficiency virus (HIV), a retrovirus, is known to cause acquired immunodeficiency syndrome (AIDS) in humans. There are two genetically related forms of HIV, HIV-1 and HIV-2. The current antiretroviral therapy (ART) may inhibit any one of the following stages of the viral infection mechanism: (i) virus adsorption to the host cell membrane, (ii) virus entry into the host cells, (iii) transformation of viral RNA into DNA, (iv) viral DNA integration with the host cell genome and (v) formation of the mature virus (which then infects other host cells). Currently used compounds for antiviral therapy belong to any one of the following classes: (a) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), (b) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (c) protease inhibitors (PIs), (d) integrase strand transfer inhibitors, (e) entry Inhibitors and (f) CCR5 antagonists blocking viral entry.

Over the past 30 years, much success in developing the anti-HIV chemotherapy regime have been observed; however, challenges remain to solve several problems related to drug-induced side effects and the emergence of drug-resistant viruses. Medicinal chemists have explored the unison of tetrazole moiety along with other existing active molecules to generate new molecules as anti-HIV agents to manage this chronic infection in a better way.

Naturally occurring L-chicoric acid (L-CA) **18** is known to selectively inhibit the integration of the viral genome inside the infected host cells. Integration of HIV DNA copy into the host cell chromosome is catalyzed by HIV integrase (IN). This integrations process is essential for the production of virus offspring. Crosby *et al.* [25] synthesized 14 compounds by combining HIV-1 integrase inhibitor (INI) L-CA with other pharmacophores and evaluated their antiviral and cytotoxic activities *in vitro*. Out of these, four compounds were tetrazole bioisosteres of L-CA and its analogues. Antiviral potencies of these tetrazole analogues were found to be enhanced compared to L-CA. Tetrazolyl analogue **19** was found to be 30-fold more potent than L-CA at relatively nontoxic concentrations.

HIV-1 attachment inhibitors interfere with the attachment of the HIV envelope glycoprotein gp120 to host cell receptor CD4. Attachment is an essential first step in the process of HIV-1 entry into host cells. Yeung *et al.* [26] synthesized heteroaryl carboxamide analogues of an early indole oxoacetic piperazinyl benzamide (HIV-1 attachment inhibitor) lead compound **20**. Tetrazole analogue **21** was found to be a potent compound (EC$_{50}$ = 0.40 nm). However, this compound was found to be poorly permeable and showed inadequate oral exposure in rats, which may be attributed to the acidic nature of tetrazolyl group. Yeung *et al.* [27] in 2013 reported another series of indole-oxoacetic piperazinyl benzamide derivatives by incorporating the heteroaryl substitution at C-7 of indole-based inhibitors of HIV-1 attachment. Out of these, a compound with fluorine group on 4-position of the indole ring and tetrazole moiety at 7-position of the indole ring **22** showed a potent antiviral activity (EC$_{50}$ = 0.08 nm) as an inhibitor of HIV-1 attachment to the host cell. Compound **22** was further evaluated for its activity against M-tropic Bal virus and the T-tropic viruses BRU and NL4-3 in cell culture and showed notable activity against JRFL-pseudotyped virus in a single cycle (EC$_{50\ \text{pdt-JRFL}}$ = 0.08 nM) [27]. Compound **22** was found to lack oral bioavail-ability in rats due to poor absorption, which was attributed to the acidic nature of tetrazole moiety. To overcome this problem, Yeung *et al.* [28] synthesized some lipophilic derivatives of compound **22** as its potential oral prodrugs **23a-c**, which were found to be potential prodrugs of compound **22**. Oral dosing of methyl analogue **23c** was found to bring about the maximum plasma concentration of compound **22**, showing that methyl analogue may be explored as a prodrug for the free NH tetrazole containing compound.

Another class of heterocyclic compounds containing aryl diketo acid (ADK) functionality are well known to be HIV INIs reported in the literature [29]. [1-(5-Chloroindol-3-yl)-3-hydroxy-3-(2*H*-tetrazol-5-yl)propanone] (5CITEP) was synthesized by Shionogi & Co. [30], is one of the notable indole derivatives in which the carboxylic function is masked by a tetrazole ring.



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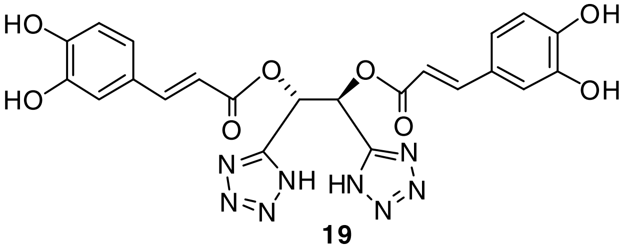

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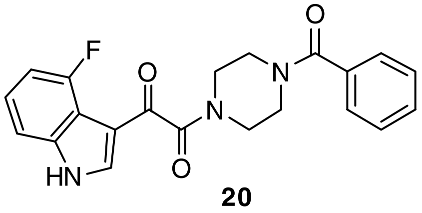

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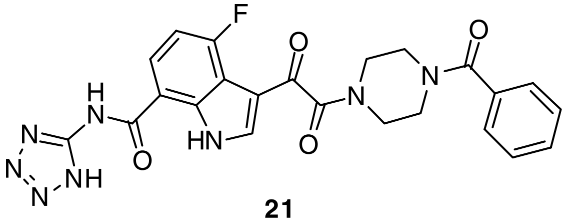

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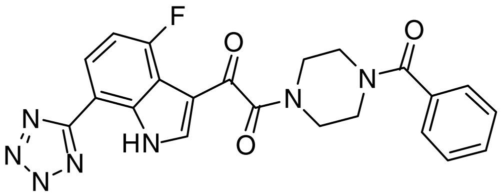

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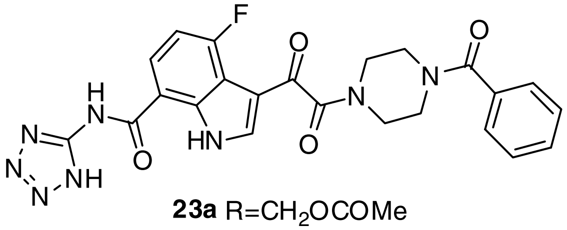
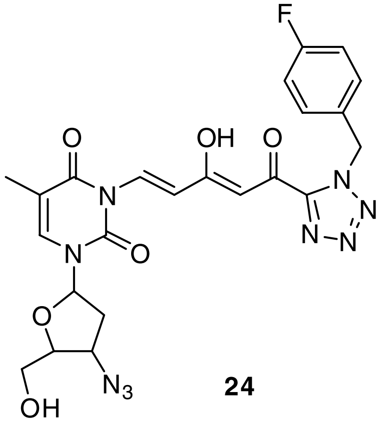


23a R=CH_2OCOMe
23b R=$CH_2COOt\text{-}Bu$
23c R=CH_3

Although 5CITEP showed potent inhibition of IN in the biochemical assays, no significant antiviral effects were observed in cellular systems [31]. In another effort to synthesize a hybrid active compound, Bosch *et al.* [32] synthesized tetrazole/1,2,3 triazole rings with azidothymidine (AZT) incorporating 1,3-dioxo moiety as a linker. The tetrazole analogue **24** was found to show low activity with HIV-1 integrase inhibitory concentration (IC_{50}) as 350 µM, where no detectable activity for the triazole analogue was found.

Earlier attempts were also made to synthesize 32-(5-amino-1,2,3,4-tetrazol-1-yl)-32-deoxythymidines (**25**) and evaluated as an anti-HIV agents [33]. Jiang *et al.* [34] reported the synthesis of a series of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTI). Among the synthesized compounds, oxindole **26** was considered as a potent inhibitor for HIV replication. However, compound **26** showed high clearance, low oral bioavailability and low exposure. In an attempt to optimize the physico-chemical properties in the desired manner, this research group synthesized a compound where they replaced the ester moiety with its bioisosteric group, tetrazole. The resultant compound did not show any activity; however, a suitably placed methyl group on the tetrazole ring analogue **27** showed an equivalent anti-HIV activity (EC_{50} = 0.055 µM) to its parent compound (EC_{50} = 0.015 µM). Researchers further synthesized a series of molecules where they replaced the ester/tetrazole moiety with other aromatic groups.

In 2006, Muraglia *et al.* [35] reported the synthesis and evaluation of a series of aryltetrazolylacetanilides. Antiviral activity (HIV-1 NNRTI) of the prepared compounds was evaluated against wild-type (WT) virus and on the clinically relevant K103N mutant strain of HIV. This investigation led to some potent compounds with nanomolar activity on K103N with oral bioavailability in rats. The most potent compound **28** showed nanomolar activity [Pol (IC_{50}) = 3 nM] against WT HIV, oral bioavailability in rats and submicromolar activity in infected cells (IC_{95}(50%NHS) = 125 nM). In 2003, Walker *et al.* [36] published a patent describing compounds bearing a triketoacid structure, as inhibitors of HIV integrase. The same research group [37] worked further to establish that diketo acid group is essential for the activity of these compounds. Upon replacing the C-terminal carboxylic acid group with its bio- isostere tetrazole in the most active triketo acid compound (IC_{50} = 9 µM) **29**, they found that that the resultant tetrazole analogue **30** lost its activity (IC_{50} = 125 9M). Such studies give an insight about careful planning for replacement of the functionalities with their bio-isosteres.



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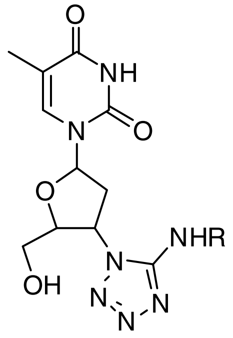
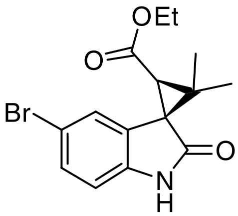


R= t-Bu, s-Bu, i-Bu, n-$C_{12}H_{25}$, $Cl(CH_2)_6$,
Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$EtOC_6H_4$

25a-i



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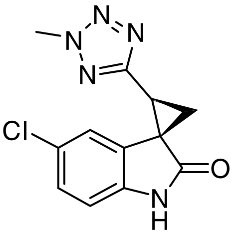

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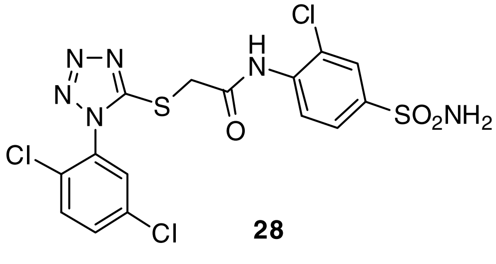

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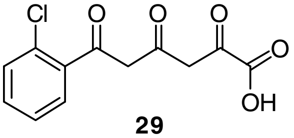

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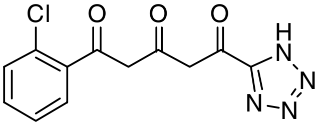

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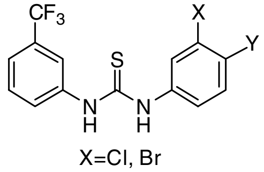
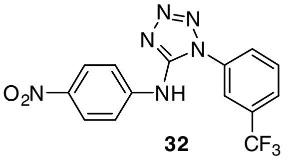
A series of thiourea derivatives **31** incorporating 3-(trifluoromethyl)phenyl moiety was synthesized by Bielenica *et al.* [38] and reported their antimicrobial and antiviral activity. In view of this observed antiviral activity, the same research group [39] modified the structure of bioactive derivatives bearing thiourea branch by introducing 1*H*-tetrazol-5-yl or 1,3-thiazolidin-4-one core in place of thiourea branch in 3-(trifluoromethyl)phenyl moiety to give 11 substituted *N*-[3-(trifluoromethyl)phenyl]-1*H*-tetrazol-5-amines (**32**). The biological activity study of these compounds did not show any anti-HIV activity and 1*H*-tetrazol-5-yl derivatives showed high cytotoxic potential.



X=Cl, Br
Y=F, Cl, H

31



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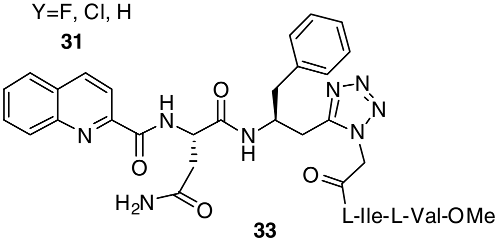

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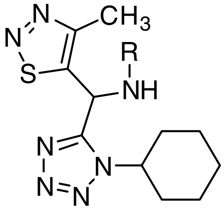
Peptidomimetics are compounds, which mimics a peptide bond to get the similar biological activity shown by the peptide compound. This has become an important tool for medicinal chemists recently. Exploring the fact that 1,5-disubstituted tetrazole ring is an excellent mimic of a *cis*-amide bond, May & Abell [40] synthesized and evaluated HIV protease inhibitory activity of a series of α-methylene tetrazole-based peptidomimetics. The most active compound of this series, (2*S*)-1-[(methyl-L-valinyl-L-isoleucinylcarbonyl)methyl]-5-[3-phenyl-2-(quinolin-2-ylcarbonyl-L-asparaginylamino)propyl]-1*H*-tetrazole (**33**), had IC_{50} = 18 μM, which was low than the base compound. The results indicate that the activity of designed peptidomimetics with tetrazole bio isostere would depend upon the interplay of geometrical factors with other substituents present in the molecule [40].

Activity against tobacco mosaic virus (TMV): Wang *et al.* [41] synthesized a series of novel tetrazole containing 1,2,3-thiadiazole derivatives **34** *via* a simplified Ugi-tetrazole reaction and easily purified them. The bioassay tests indicated that most target compounds showed higher anti-TMV activity compared to ribavirin at 100 mg/mL.

Activity against herpes simplex virus (HSV): Abdel-Aal *et al.* [42] synthesized tetrazolyl derivatives **35** and **36**, which showed antiviral activity against herpes simplex virus type-1 (HSV-1) and Hepatitis-A virus (HAV, MBBcell culture-adapted strain).



R= isopropyl, cyclopropyl, 2-fluorophenyl

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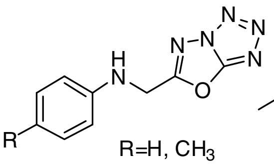

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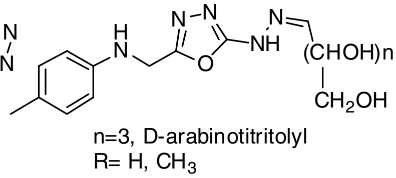

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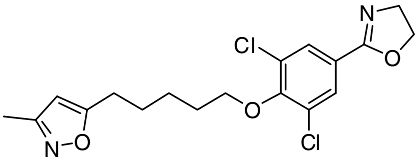
Activity against picornavirus: The picornavirus virion is an icosahedral, non-enveloped, small (22 to 30 nm) particle. The capsid proteins encase a sense RNA strand consisting of approximately 7,500 nucleotides. The RNA carries a covalently bound non-capsid viral protein (VPg) at its 52 end and a polyadenylated tail at its 32 end. Diana *et al.* [43] synthesized a series of tetrazole analogues of a broad-spectrum antipicornavirus drug Win 54954, compound **37** to address the acid lability of the oxazoline ring. Compound **38**, with a three-carbon linkage between the isoxazole and phenyl rings and a propyl chain extending from the isoxazole ring, exhibited MIC_{80} for 15 rhinovirus serotypes of 0.20 1M as compared to 0.40 pM for compound **37**. The propyl side chain of compound **38** extends into a pore in the binding site with the possibility of hydrophobic interactions with a pocket formed by Leu106 and a portion of Ser107 in human rhinovirus-14 as reported in the X-ray studies [43]. 2-Methyltetrazole derivative **39** possessed a similar activity profile to the oxazoline series, but was found to cause hepatoxicity *in vivo* and was abandoned from further development [44].

Activity against enterovirus: Enterovirus D68 (EV-D68) is a respiratory viral pathogen that primarily infects children



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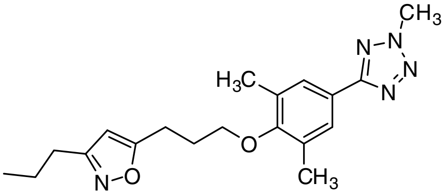

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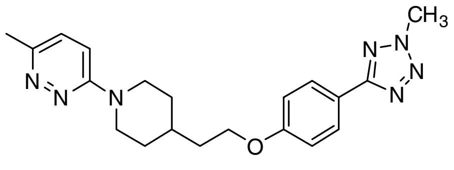
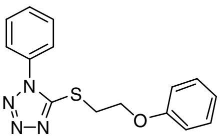


39

under age group of eight. Although EV-D68 infection typically leads to moderate to severe respiratory illnesses. Ma *et al.* [45] reported the discovery of a viral capsid inhibitor R856932, a tetrazole compound **40** inhibits multiple contemporary EVD68 strains with single-digit to submicromolar efficacy. Compound **40** binds to the hydrophobic pocket of viral capsid protein VP1, thereby preventing viral uncoating and release of viral genome in the infected cells. Compound **41** exhibited a strong activity against Human enterovirus 71 (EV71) with no significant cellular toxicity [46].



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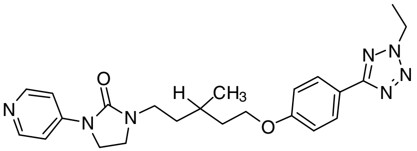


41

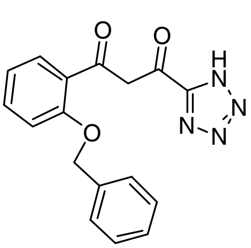
Activity against hepatitis C virus (HCV): Hepatitis C virus (HCV) is known to cause hepatitis C liver infection. HCV spreads when contaminated blood enters the bloodstream of another person, mostly through sharing needles or other equipment used to inject drugs and blood transfusion. HCV is a small, hepatotropic RNA virus. In some cases, victims may clear out the virus from their bodies in six months, but mostly, it presents itself as a chronic infection. HCV treatment regime focuses on eradicating the virus from an infected person to prevent the progression of liver diseases, cirrhosis, fibrosis and hepatocellular carcinoma. Anti-HCV drugs fall under four major chemotherapy classes: (i) non-specific antivirals, (ii) NS3 (nonstructural protein 3)/4A protease inhibitors, (iii) NS5B (nonstructural protein 5B) polymerase inhibitors and (iv) NS5A (nonstructural protein 5A) inhibitors.

Song *et al.* [47] designed, synthesized and evaluated a series of diketo tetrazoles and diketo triazoles as bioisosteres of α,γ-diketo acid inhibitors of HCV polymerase NS5B. All the synthesized compounds were evaluated for their anti-HCV activities and cytotoxicity in an authentic HCV infection/replication system (human hepatoma cell lines Huh-7) at the single concentration of 50 μM. Out of the synthesized tetrazole analogues, one compound 2-(benzyloxy)phenyl diketo tetrazole (**42**) showed considerable anti-HCV activity (EC_{50} = 9.2 μM), though the best compound in this series was a triazole analogue with an EC_{50} value of 3.9 μM [47].

In 2003, Perni *et al.* [48] reported a compound **43** with good nonstructural protein 3 (NS3) protease inhibitory activity relevant to anti-HCV properties. Sun *et al.* [49] replaced the carboxylic acid group from P4 terminus of **43** to synthesize compound **44** which showed excellent NS3 protease enzyme inhibitory potency (K_i = 6 nM) when evaluated in the pNA (peptide nucleic acid) based enzyme inhibition assay against truncated NS3 enzyme. Miao *et al.* [50] filed a patent that covers 1,5-disubstituted tetrazole derivatives inhibiting serine protease activity, particularly the activity of hepatitis C virus (HCV) NS3-NS4A protease.

Activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Although considerable number of SARS-CoV-2 vaccines in place now, still effective drugs as better treatment options for affected patients are required. The severity of COVID-19 has instigated researchers to discover new molecules and at the same time evaluate already existing bioactive molecules, especially antiviral, for their activity against SARS-CoV-2. In a theoretical attempt, Cortés-García *et al.* [51] performed an *in silico* assay for anti-SARS-CoV-2 activity of 1,5-disubstituted tetrazole-1,2,3-triazoles (**45**). The computer-based study was done on CoV-2-M^{Pro}, which is the main protease of SARS-CoV-2. Based on the docking results obtained from the study considering a pharmacophore model, Aguilar-Morales *et al.* [52] also proposed a series of ten 1,5-disubstituted tetrazole-1,2,3-triazoles **46a-h**, **47**, **48** as potent inhibitors of CoV-2-M^{Pro}. The pharmacophore model prepared by Cortés-García *et al.* [51] also revealed that (i) compound **47** has a high potential in the design of new drugs against the SARS-CoV-2 and (ii) hydrophobic and stacking interactions play a key role in the design of new drug candidates based on this pharmacophore model.

Angiotensin converting enzyme 2 (ACE 2) catalyses the formation of angiotensin-(1-7) from angiotensin II as an important step in human physiological processes. ACE 2 receptor is



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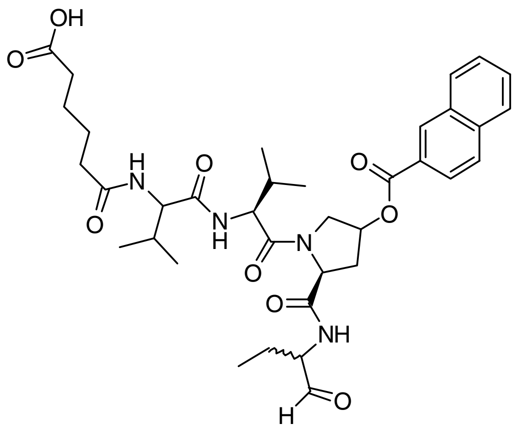

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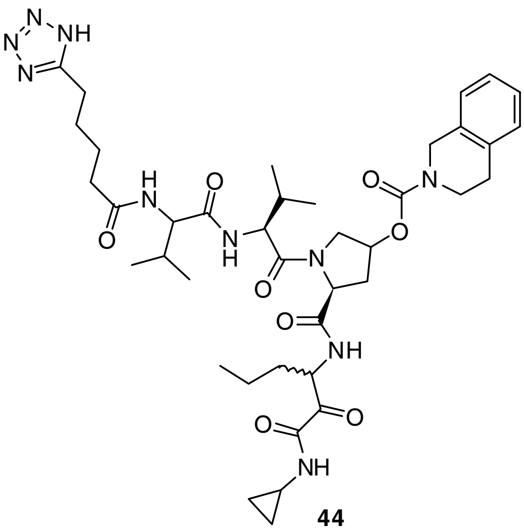

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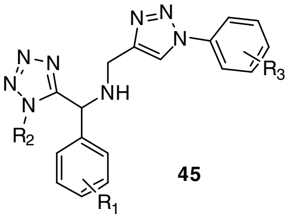

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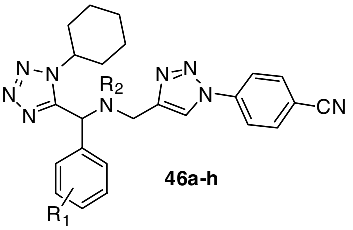
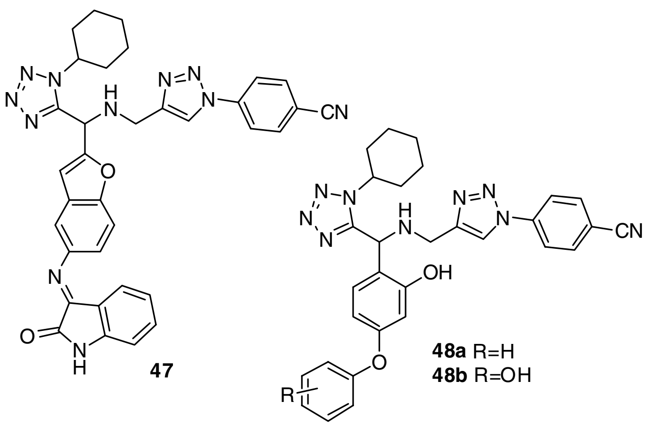


46a-h

46a R_1=4-Phenoxy, R_2=COOH
46b R_1=4-Phenoxy methyl, R_2=COOH
46c R_1=4-pyridyl, R_2=COOH
46d R_1=2-pyridyl, R_2=COOH
46e R_1=2-pyridyl,R_2=H
46f R_1=4-pyridyl, R_2=H
46g R_1=4-Phenoxy methyl, R_2=H
46h R_1=4-Phenoxy, R_2=H



47

48a R=H
48b R=OH

attached to the cell membrane of several organs. The SARS-CoV-2 interacts first through ACE 2 receptor while infecting humans. The spike glycoprotein, present on SARS-CoV-2 outer structure binds to ACE 2 and facilitates virus entry into the human cell, is a potential target for developing specific drugs, antibodies and vaccines against COVID-19 [53].

SARS-CoV-2 infection and its spike protein reduce ACE 2 expression in lungs, causing acute effects on lung and, in worst case, lung failure. This suggests that ACE 2 antagonists/blockers can be considered as a rational option for COVID-19 therapy. Several inhibitors of ACE 2 have recently been reported as anti-SARS-CoV-2 agents [54]. Losartan **49**, an ACE 2 antagonist used for high blood pressure treatment, have been proposed as a suitable drug against COVID-19. Though Losartan cannot block the virus, it may reduce the activity of the renin-angiotensin system alleviating the severity of the disease [55].

Conclusion

Tetrazole based scaffolds are a prime class of heterocycles due to their isosteric character to carboxylic acid and *cis*-amide functional groups, further supported by their metabolic stability and other favourable physico-chemical properties. There is an immense potential of tetrazoles to generate biologically active compounds including antiviral compounds. This review article has presented comprehensive activity details of tetrazole analogues prepared by adding tetrazolyl moiety into adamantane, natural substances, peptides, nucleosides and terpenes, as promising agents for the development of antiviral activity. Extensively planned and focused investigations need to be carried out to evaluate activities of tetrazole based compounds as various antiviral agents. The present review can set up a direction for the future design and development of novel tetrazole containing antiviral therapeutics with broader spectrum, higher efficiency and lower toxicity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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