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REVIEW OF THE LATEST RESEARCH ON THE ANTIVIRAL POTENTIAL OF 1, 2, 4-TRIAZOLE DERIVATIVES

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ABSTRACT

1,2,4-Triazoles are heterocyclic organic compounds with a broad spectrum of biological activity, including antiviral properties. The advantages of 1,2,4-triazole derivatives as a “core framework” for antiviral compounds include chemical stability, which ensures high resistance to hydrolysis and oxidation, sufficiently high bioavailability, and the potential for chemical modification, among others. Therefore, the search for new 1,2,4-triazole derivatives with antiviral activity remains a relevant task in modern pharmaceutical science. The aim of this study was to analyze and summarize global advancements in recent years regarding the study of antiviral properties of 1,2,4-triazole derivatives and to substantiate the necessity and feasibility of further research in this area. 1,2,4-Triazole is a significant heterocyclic “framework" actively studied in medicine and pharmacy due to its wide range of biological activities, including antiviral properties. Investigating the influence of functional groups in the triazole structure on its antiviral properties enables the development and implementation of effective drugs. Modifying functional groups in the 1,2,4-triazole molecule allows for the modulation of its activity. Careful structural planning using molecular docking and screening methods facilitates the creation of effective medications against various viruses. **Conclusion:** Global advancements in the study of antiviral properties of 1,2,4-triazole derivatives in recent years have been analyzed and summarized. The necessity and feasibility of further research in this chosen direction of scientific inquiry have been substantiated.

KEYWORDS: 1,2,4-triazole, heterocyclic systems, viruses, antiviral activity, in silico studies, triazole properties, biological activity.

INTRODUCTION

1,2,4-Triazoles are heterocyclic organic compounds with a broad spectrum of biological activities, including antiviral properties. Due to their structural features, they can bind to various viral proteins or block key stages of the viral life cycle, making them promising candidates for the development of new antiviral drugs. Many derivatives of 1,2,4-triazoles can disrupt the replication process of viral DNA or RNA by inhibiting enzymes such as DNA or RNA polymerases and viral proteases. These compounds can also interact with viral proteases responsible for cleaving viral polyproteins into functional proteins necessary for viral assembly. Additionally, certain derivatives of this heterocyclic class are capable of enhancing the activity of interferons or other components of the immune system, thereby increasing the body's resistance to viral infections. Triazoles may also interact with proteins or lipids of the cell membrane, blocking the virus from binding to target cell receptors. The advantages of 1,2,4-triazole derivatives as a “core framework” for antiviral compounds include chemical stability, which ensures high resistance to hydrolysis and oxidation, high bioavailability, and the potential for chemical modification. For these reasons, the search for new 1,2,4-triazole derivatives with antiviral activity remains a relevant challenge in modern pharmaceutical science. Special attention should be given to the development of triazole-based drugs against emerging viruses such as SARS-CoV-2, West Nile virus, and Ebola virus. The use of computer modeling (in silico) and chemical synthesis significantly simplifies the search for new effective molecules. Taken together, these factors make 1,2,4-triazoles an important class of compounds for the creation of innovative antiviral agents. The **aim** of this study was to analyze and summarize global achievements in recent years regarding the study of the antiviral properties of 1,2,4-triazole derivatives and to substantiate the necessity and feasibility of further research in this chosen area of scientific inquiry.

MATERIALS AND METHODS

Triazole frameworks play a significant role in exhibiting a wide range of biological properties, demonstrating

excellent antiviral activity in both nucleoside analogs and non-nucleoside compounds. In this review, the authors have summarized new synthetic methods developed by various research groups and provided a comprehensive description of the potential of 1,2,4-triazole derivatives as antiviral agents.[1] It has been shown that antiviral triazole compounds affect a wide range of molecular proteins. Furthermore, several viral strains, including human immunodeficiency virus (HIV), SARS virus, hepatitis B and C viruses, and influenza virus, have been found to be sensitive to triazole derivatives. N-heterocycles play a crucial role in studying antitumor, anti-inflammatory, antibacterial, antiviral, antidiabetic, and other properties.[2] In the presented work, the authors focus on studying certain 5- or 6-membered N-heterocyclic compounds that have demonstrated antiviral activity, as well as exploring the structure-activity relationships of these compounds.

RESULTS AND DISCUSSION

SARS-CoV-2 has caused tens of thousands of infections and over a thousand deaths. Currently, there are no approved drugs for the treatment of coronavirus infections. In this study, researchers systematically analyzed all proteins encoded by SARS-CoV-2 genes, compared them with proteins from other coronaviruses, predicted their structures, and constructed 19 structures using modeling techniques.[3]

By performing virtual ligand screening based on target proteins, a total of 21 targets (including two human targets) were evaluated against compound libraries, including the ZINC drug database. The structure and screening results for critical targets, such as 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and papain-like protease (PLpro), were thoroughly investigated by the authors. These studies provide new opportunities for the development of drugs to treat SARS-CoV-2 infections.

The four endemic human coronaviruses, HCoV-229E, -NL63, -OC43, and -HKU1, account for a significant proportion of upper and lower respiratory tract infections in adults and children. While their clinical presentation resembles that of many other common cold pathogens, their evolutionary history and host associations offer valuable insights into the natural history of past human pandemics.[4]

As researchers assert, the bovine coronavirus is considered a potential ancestor from which HCoV-OC43 may have originated during a pandemic historically recorded in the late 19th century.[4] New evidence suggests that HCoV-229E may actually be transmitted from dromedary camels, similar to the Middle East Respiratory Syndrome coronavirus (MERS). This scenario provides important ecological parallels to the current pre-pandemic model of host associations with the MERS coronavirus.

Another research group developed and synthesized a series of novel derivatives. All compounds were evaluated in vitro for their neuraminidase (NA) inhibitory activity against influenza A (H1N1) virus.[5] The results showed that most target compounds exhibited moderate to good NA inhibitory activity. One compound demonstrated the most potent inhibitory activity, with an IC50 value of 13.06 μM against the H1N1 influenza subtype. Structure-activity relationship (SAR) analysis revealed that introducing methoxy groups to substituted benzylmethylene significantly enhanced the compounds' activity. This study provides valuable insights for the development of new drugs against influenza viruses, including mutant strains.

Compounds containing thiazole and triazole are widely recognized for their antibacterial, antifungal, anti-inflammatory, antimalarial, antituberculosis, antidiabetic, antioxidant, anticonvulsant, and antitumor activities, among others.

The aim of this study is to summarize recent advancements in the discovery of biologically active compounds among thiazole and triazole derivatives.[6] Structural biology has emerged over the past three decades as a powerful tool for rational drug discovery. Crystalline structures of biological targets, both in isolation and in complexes with ligands and inhibitors, provide significant insights into enzyme mechanisms, conformational changes during ligand binding, and the architecture and interactions of binding pockets.

Structural methods, such as crystallographic fragment screening, are invaluable tools today for identifying new biologically active compounds. In this context, three-dimensional protein structures play a crucial role in understanding activity and developing new antiviral agents against various viruses.[7]

This study analyzes the evolution of the resolution of viral structures and the role of crystalline structures in the discovery and optimization of new antiviral agents. To address the challenge of treating SARS-CoV-2 viral infections, researchers have created a combinatorial library of fluorogenic derivatives.[8] A potent SARS-CoV-2 inhibitor was synthesized by the authors. SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is the etiological agent responsible for the global outbreak of COVID-19 (coronavirus disease 2019).

The main protease of SARS-CoV-2, Mpro, is a key enzyme that plays a crucial role in mediating viral replication and transcription. A team of scientists developed and synthesized two compounds specifically targeting Mpro.[9] Both compounds demonstrated excellent inhibitory activity and strong efficacy against SARS-CoV-2 infection. X-ray crystalline structures of SARS-CoV-2 Mpro in complex with the compounds, resolved at a resolution of 1.5 Å, showed that the aldehyde groups of the compounds covalently bind to

cysteine 145 of Mpro. These compounds exhibited excellent pharmacokinetic profiles and low toxicity, indicating their potential as promising drug candidates.

The outbreak of coronavirus disease 2019 (COVID-19) has resulted in a global pandemic due to the rapid spread of SARS-CoV-2. The study reports the synthesis of a potent compound that inhibits SARS-CoV-2 replication in Vero E6 and other cell lines.[10] Experiments in mice infected with the murine hepatitis virus, a closely related coronavirus, demonstrated that the compound was highly effective in reducing viral titers in infected CoV organs without noticeable toxicity.

Chronic hepatitis B (CHB) is one of the leading causes of morbidity and mortality worldwide. Currently, clinically approved nucleoside analogs (NAs) are highly effective in combating the hepatitis B virus. However, prolonged use of antiviral drugs contributes to the emergence of potential drug resistance. To address this issue, combination therapy is often employed, but progressively altered mutations remain a threat.

To tackle this challenge, a team of researchers successfully synthesized 2'-fluoro-6'-methylene-carbocyclic adenosine (FMCA) and its phosphoramidate derivative (FMCAP), which can be used in combination therapy to treat drug-resistant chronic hepatitis B.[11]

In addition to nucleosides, other synthetic derivatives with antiviral activity deserve attention, as well described in.[12] The article presents, for the first time, a comprehensive classification of such antiviral drugs and candidate compounds, summarizing their biological targets and clinical applications. The described compounds are organized by their antiviral mechanisms of action.

Understanding the activity of a compound against specific molecular targets can be key to developing new antiviral drugs. The article also briefly discusses future directions in antiviral therapy. The examples of antiviral compounds described may be valuable for the further development of medicines.[13, 14]

Thio-substituted 1,2,4-triazoles are highly intriguing compounds due to their significant role in cancer treatment. Moreover, researchers have demonstrated that they can serve as promising antiviral agents.[15] The following literature review summarizes data on the antiviral activity of 1,2,4-triazole derivatives.[16] A comprehensive compilation of studies conducted over the past decade on the 1,2,4-triazole core provides a broad foundation for researchers to advance new potential drug candidates with improved efficacy and selectivity.

In recent decades, researchers have focused on condensed heterocycles, as these exhibit better pharmacological effects compared to standalone triazoles.[17] The presented study involves the synthesis of 1,2,4-triazole derivatives with N-bridged bonds that exhibit potent antiviral properties. Domestic researchers have determined that **piperidinium 2-[5-(furan-2-yl)-2H-1,2,4-triazol-3-ylthio]acetate** most effectively inhibits vesicular stomatitis virus (VSV) replication when added to the culture medium simultaneously with cell monolayer infection.[18]

In this case, the compound achieves maximum efficiency when present in the medium for 72 hours, reducing VSV infectious activity by more than 6.5 lg TCID50/mL compared to the control. When the compound is added two hours post-VSV adsorption, the highest antiviral activity is observed 120 hours post-infection, with a reduction in VSV infectious activity exceeding 4.75 lg TCID50/mL.

Also noteworthy is a review article that summarizes literature on the study of the antiviral activity of drugs and new substances based on 1,2,4-triazole.[19]

The prevalence of viruses is largely explained by their rapidly mutating RNA genomes, which allow infections to persist. RNA genomes of infections contain RNA-dependent RNA polymerase (RdRp), a key enzyme facilitating RNA synthesis. Thus, RdRp is a critical therapeutic target for the development of new, effective drugs. The study demonstrates the efficacy of novel compounds combining the triazole fragment with other functional groups.[20]

The review also describes RdRp inhibitors that have been launched or are currently undergoing clinical trials for the treatment of RNA-virus infections.

In summary, it should be noted that 1,2,4-triazole is a crucial heterocyclic “framework” that is actively studied in medicine and pharmacy due to its broad spectrum of biological activity, particularly its antiviral properties. Research into the impact of functional groups on the triazole structure and their antiviral properties enables the development and implementation of effective drugs.

For example: Alkyl groups (e.g., methyl, ethyl) at positions 3 or 5 of the triazole ring generally enhance the molecule's lipophilicity, facilitating penetration through cell membranes, which may improve antiviral activity. Aryl substituents (e.g., phenyl radicals) increase activity by enhancing molecular interactions with viral proteins through π–π stacking. The presence of halogen atoms (F, Cl, Br, I) in the molecule improves lipophilicity and metabolic stability. Fluorinated derivatives often exhibit strong antiviral activity due to bond polarization effects.[21]

Hydroxyl groups can form hydrogen bonds with amino acid residues in the enzymatic centers of viral proteins. This often enhances the antiviral effect; however, excessive polarity may reduce membrane penetration.

Primary, secondary, and tertiary amines improve binding with viral nucleic acids or viral enzymes. Modifying the amino group (e.g., into guanidine derivatives) can significantly enhance antiviral activity. Nitro and cyano groups can participate in specific electrostatic interactions with viral enzymes, contributing to their antiviral potential.

However, their presence may increase the toxicity of compounds. Sulfonyl derivatives of 1,2,4-triazole often exhibit enhanced antiviral activity due to their strong electron-donating or electron-withdrawing effects, which promote interactions with the active sites of viral proteins.

The introduction of other heterocycles (e.g., pyridine, furan, or imidazole) into the triazole structure broadens the spectrum of antiviral activity by improving interactions with biological targets.[22] Carboxylic acids or their esters enhance solubility and binding to viral enzymes, particularly RNA-dependent RNA polymerases.[22] The use of acyclic or cyclic substituents is often applied to target specific viruses. For instance, acyclic derivatives of 1,2,4-triazole may be active against HIV or influenza.

Thus, modifying the functional groups within the 1,2,4-triazole molecule allows for the modulation of its activity.[23, 24] Careful structural planning using molecular docking and screening methods facilitates the development of effective drugs against various viruses.

CONCLUSION

Global advancements in recent years regarding the study of antiviral properties of 1,2,4-triazole derivatives have been analyzed and summarized. The necessity and feasibility of further research in this chosen direction of scientific inquiry have been substantiated.

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