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HETEROCYCLES IN FOCUS

Antiviral activity of 1,2,4-triazole derivatives (microreview)

Nataliia V. Simurova[1]*, Olena I. Maiboroda[1]

[1] *National University of Food Technologies,*
68 Volodymyrska St., Kyiv 01601, Ukraine; e-mail: n.v.simurova@gmail.com

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The microreview summarizes data published since 2015 on the antiviral properties and synthesis of compounds containing the 1,2,4-triazole ring.

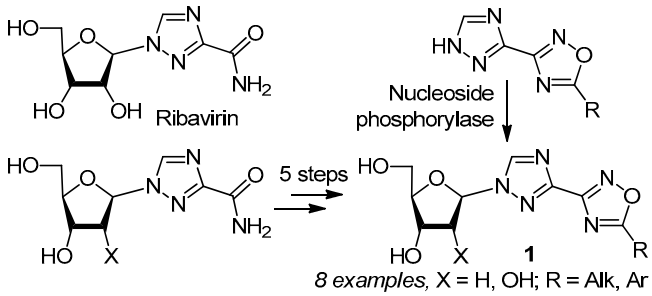
Introduction

Today, 1,2,4-triazole derivatives are the preferred structural moieties in the development of new drugs with a wide range of pharmacological activity, as evidenced by several reviews.[1] This is due to the fact that the triazole ring can be considered a bioisostere of an amide, ester, or carboxyl groups.[2] Relatively low toxicity, good pharmacokinetic and pharmacodynamic properties of triazole, its resistance to metabolic degradation are another advantages. In recent years, against the background of the emergence of new viral infections and the lack of effective chemotherapeutic agents for their treatment, the number of studies on the antiviral properties of 1,2,4-triazole derivatives has significantly increased. In the presented review, we focused on current publications devoted to the study of the antiviral properties of compounds containing the 1,2,4-triazole ring. Isosteric analogs of known drugs, as well as new molecules, are considered.

Analogs of ribavirin and doravirine

Ribavirin has antiviral activity against RNA and DNA viruses (hepatitis C, influenza A and B, herpes type 1 and 2 viruses, etc.). The possibility of using this compound for the treatment of hantavirus, various hemorrhagic fevers, as well as coronavirus is currently being evaluated.[3] Various mechanisms of action of ribavirin have been proposed. This molecule is thought to have different effects on different viruses. According to one hypothesis, ribavirin is an imitator of the purine guanosine cycle.[4]

Zhurilo et al.[5] proposed two methods for the synthesis of ribavirin analogs **1** (chemical and chemoenzymatic methods starting from natural nucleoside substrates) by replacing the carboxamide fragment with the isostere 1,2,4-oxadiazole ring. The obtained compounds demonstrated high activity against viruses of hepatitis C, herpes simplex type 1, influenza A, comparable to the effect of ribavirin.

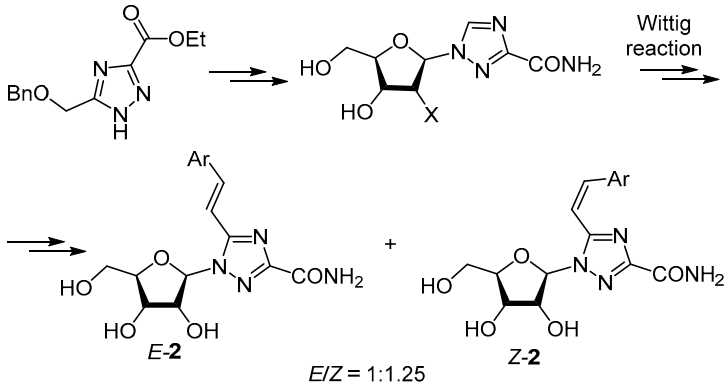


Nataliia V. Simurova is Associate Professor at the Department of Food Chemistry of the National University of Food Technologies (Kyiv, Ukraine). She completed her PhD thesis in Chemical Sciences carried out under the guidance of Professor A. D. Sinitsa and defended it in 1995 at the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Her research interests include chemistry of heterocyclic compounds, chemistry of trivalent phosphorus derivatives, and medicinal chemistry.

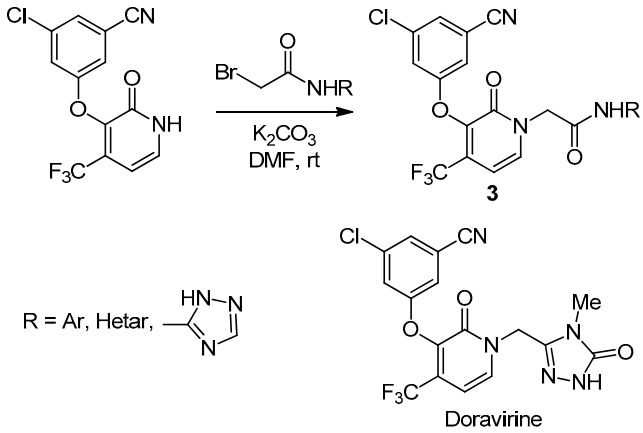
Olena I. Maiboroda is Associate Professor at the Department of Food Chemistry of the National University of Food Technologies (Kyiv, Ukraine). She completed her PhD thesis in Chemical Sciences carried out under the guidance of Professor A. I. Tolmachev and defended it in 2002 at the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Her scientific interests include synthesis of biologically active oxygen- and nitrogen-containing heterocyclic compounds, chemistry of polymethine dyes.

Analogs of ribavirin and doravirine (continued)

A series of studies by Chudinov et al.,[6] Tang et al.[7] is devoted to the synthesis of ribavirin analogs **2** containing a vinylaryl substituent at position 5 of the triazole ring. The relationship between the structure and activity of the obtained compounds *E*/*Z*-**2** in regards to hepatitis C, influenza, and herpes simplex viruses was studied. The obtained results[6] indicate that all active compounds have common features: a rigid bond between the triazole and aryl rings, lipophilic substituents in the *para* position of the aryl ring. It was demonstrated that only the *E*-isomers possess high activity against herpes simplex virus comparable to the activity of ribavirin, while the *Z*-isomers are inactive.

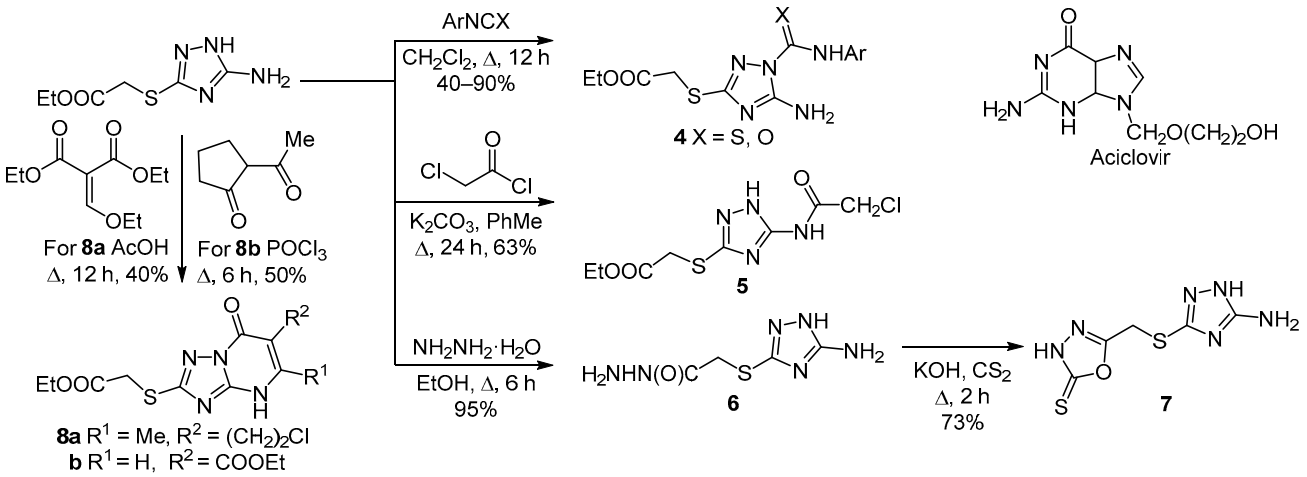


Wang et al.[8] synthesized a series of acetamide-substituted analogs of doravirine, a potent non-nucleoside reverse transcriptase inhibitor (NNRTI). Most of the obtained compounds **3** had inhibitory properties against HIV-1. Compound **3** with the 1,2,4-triazole substituent in the amide fragment showed excellent efficacy, comparable to that of doravirine and significantly superior to that of lamivudine, with high selectivity.



Acyclovir isosteres

Acyclovir is the ancestor of antiherpetic drugs – blockers of viral DNA synthesis. A series of isosteric analogs of acyclovir **4**–**8** containing the 1,2,4-triazole ring was obtained.[9] It was shown that derivatives substituted both at the endocyclic (compounds **4**) and exocyclic (compound **5**) nitrogen atoms are active against herpes simplex type 1 virus. Condensed triazolopyrimidines **8**, which are structurally similar to purine bases, showed the highest activity with high selectivity and low toxicity. The authors of the study[9] believe that the lipophilicity of the substituents R^1 and R^2 is also an important factor determining the antiviral activity. As a result of physicochemical studies using the ADMET principle,[10] it was established that the closest analog of acyclovir, compound **8a**, is a promising candidate for further development as an antiherpetic agent. It has also been shown[9] that the replacement of the triazole ring with a thiadiazole one leads to the complete loss of antiviral activity. The introduction of the oxadiazole ring into compound **7** did not bring the desired result either.

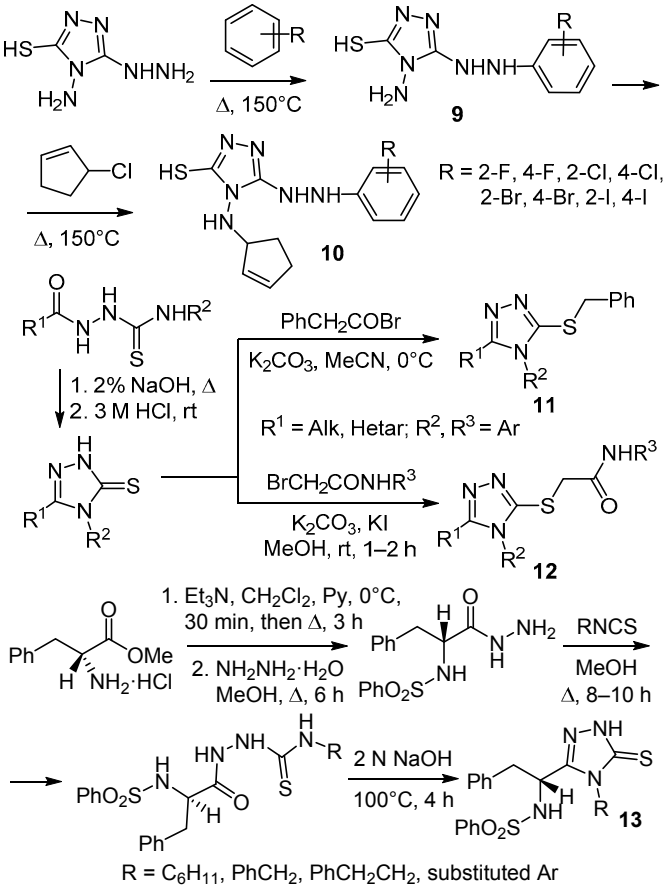


Substituted triazolethiones and thiols

Recently, Zaher et al.[11] synthesized a number of 4-amino-5-hydrazine-4*H*-1,2,4-triazole-3-thiol derivatives **9**, **10** while searching for effective inhibitors of the Nsp13 helicase of the MERS coronavirus. It was shown that the most active compounds are those containing halogen atoms in the *para* position of the aryl substituent and the cyclopentene fragment.

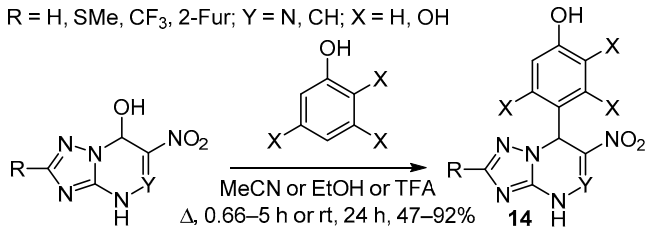
Frączek et al.[12] synthesized a number of compounds **11**, **12** based on 3,4-disubstituted triazole-5-thione. Compound **12** (R^1 = Me, R^2 = 4-carboxy-2-chlorophenyl, R^3 = benzyl) showed high activity against HIV-1 and good pharmacokinetic properties. The authors believe that it may serve as the basis for the development of powerful new triazole NNRTIs for the treatment of HIV-1.

A series of optically pure derivatives of 1,2,4-triazole-3-thiones **13** with a benzenesulfonamide group was synthesized by Başaran et al.[13]
All compounds were tested for activity against a wide range of DNA and RNA viruses, including various strains of herpes simplex virus and HIV, as well as influenza A (H1N1, H3N2) and B viruses, varicella zoster virus, human cytomegalovirus, etc. It was demonstrated that enantiomers of 1,2,4-triazole-3-thiones of the *R*-configuration with electron-withdrawing substituents are potential candidates for the development of drugs against influenza A (H1N1) viruses, while the *S*-enantiomers do not exhibit antiviral activity.



Condensed triazole derivatives

Condensed 1,2,4-triazole derivatives possess a variety of biological activities, including antiviral activity, and therefore arouse considerable research interest. Stable σ-adducts of 1,2,4-triazolo[5,1-*c*]triazines and 1,2,4-triazolo-[1,5-*a*]-pyrimidines **14** with various polyphenols were obtained and their antiviral activity was investigated.[14] Triazoloazines modified with fluoroglycine have the greatest activity against influenza A (H1N1) virus. Molecular modeling has shown that their action is directed against viral hemagglutinin, a protein that ensures the ability of the virus to attach to the host cell.



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