Viral infections cause diseases in humans, animals, and even plants. Plant viruses are frequently spread from plant to plant through insects, whereas some viruses of animals, including humans, are spread by exposure to infected body fluids. Viruses such as influenza, norovirus, rotavirus, dengue, human immunodeficiency virus (HIV) are frequently transmitted by cough, sneeze, contamination-infected food, blood-sucking insects, and through sexual contacts. Within the last five years two major outbreaks of Ebola virus have happened in Africa, Zika virus has spread throughout the Americas, and recently a novel coronavirus (2019-nCoV) has been diagnosed in people.

Antibiotics have no effects on viruses, whereas antiviral drugs have been recognized to treat life-threatening infections. Vaccines that produce life-long immunity can preclude some viral infections. In recent years several important viral infections have emerged and antiviral chemotherapeutic agents are not sufficiently effective in clinic, leading to serious human diseases and mortality. Therefore, novel antiviral candidates are urgently desirable, which undoubtedly is essential for the therapy of various fatal and debilitating viral infections. Heterocyclic compounds are obtaining importance in the field of medicinal chemistry because of the broad spectrum of their physiological activities. Among N- and S-containing heterocycles, indole, imidazole, thiazole, pyridine, and quinazoline derivatives are especially attractive. The present review highlights antiviral behavior of these heterocyclic compounds.

Keywords: antiviral activity, biological activity, cytotoxicity, virus.
| Heterocyclic fragment | Name of the compound | Virus type | Reference |
|-----------------------|-----------------------|------------|-----------|
| **Indole** | 5-(1H-Indol-3-yl)-1-phenyl-N-(4,5,6,7-tetrahydro-1,3-dioxoisodindol-2-yl)-1H-pyrazole-3-carboxamide (1a) | HSV-1 | 12 |
| | 2-(E)-1-(1H-Indol-3-yl)methylene[4-hydrazone]-5-[(E)-4-chlorophenyl]diazenyl]-4-methylthiazole (1b) | HSV-1 | 12 |
| | 2-Hydroxyproparazo[1,2-a]indole-3(2H,3H)-dione (1c) | IAV, HCV | 13 |
| **Isoindole** | (5S)-9b-(4-Chlorophenoxy)-1-nicotinoyl-1,2,3,9b-tetrahydro-5H-imidazo[1',2':1,2]pyrrole[3,4-c]pyridin-5-one (BTA9881) (2a) | RSV | 14 |
| **Pyrazole** | 6-Chloro-9-fluoro-3-phenyl-3H-benzol[b]pyrazolo[3,4-b][1,6]naphthyridine (3a) | HSV-1 | 15 |
| | 1-(4-Chlorophenyl)-3-methyl-5-phenyl-5,6-dihydropyrrolo[3,4-c]pyrazol-4(1H)-one (3b) | BVDV | 16 |
| **Imidazole** | N,N',1-Trimethyl-2(thiazol-4-yl)-1H-benzol[d]imidazo-5-carboxamide (4a) | HBV | 17 |
| | (Z)-2-(2-Methyl-5-nitro-1H-benzol[d]imidazo-1-yl)-3-(5-methyl[2-furan-2-yl]-1-phenylprop-2-en-1-one (4b) | RVA, HAdV7 | 18 |
| | 2-(2-Methyl-5-nitro-1H-benzol[d]imidazo-1-yl)-1-phenyl-3-thiophen-2-yl)-prop-2-en-1-one (4c) | | |
| **Imidazo-pyridine** | 3-[[1,1'-Biphenyl]-3-yl]-2-(4-fluorophenyl)-6-(phenylsulfanyl)imidazo[1,2-a]pyridine (5a) | HCV, BVDV | 19 |
| | 3'-(2-Methoxynaphthenyl)-6-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetate (5b) | | |
| **Indazole** | 2-(7-(4-Fluorobenzylidene)-3-(4-fluorophenyl)-5-phenyl-4,5,6,7-tetrahydro-2H-indazol-2-yl)-7-methylbenzo[d]thiazole (6a) | CV-B4, RVA, HAdV7 | 20 |
| | 2-[7-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-5-phenyl-4,5,6,7-tetrahydro-2H-indazol-2-yl]-7-methylbenzo[d]thiazole (6ab) | | |
| | 2-[7-(2,6-Dimethoxybenzylidene)-3-(2,6-dimethoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-2H-indazol-2-yl]-7-methylbenzo[d]thiazole (6b) | | |
| **Thiazole** | 2-(4-Bromobenzolyl)imidazo[2,1-b][1H]-imidazole-5-(5-[3aR,5S,6R,6aR]-6-methoxy-2,2-dihydropyrazolofuro[2,3-d][1,3]dioxol-5-yl)methanone (7aa) | JUNV | 21 |
| | 2-(4-Chlorobenzolyl)imidazo[2,1-b][1H]-imidazole-5-[5-[3aR,5S,6R,6aR]-6-methoxy-2,2-dimethylthiapyrazolofuro[2,3-d][1,3]dioxol-5-yl)methanone (7ab) | | |
| | (2F,5S)-5-(3-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-yldiene)-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)thiazol-2-yl]imino]-3-phenylthiazolidin-4-one (7b) | HCV | 22 |
| | (6R,7S)-7-(4-Ethoxyphenyln)-2-oxo-5,3,6,7-tetrahydro-2H-thiopryan-2,3-dil[thiazol-6-carbaldehyde (7ca) | EBV | 23 |
| | 4-(6,7,5S)-6-Formyl-2-oxo-3,5,6,7-tetrahydro-2H-thiopyran-2,3-dil[thiazol-7-yl]benzol (7eb) | HCV, IAV | 24 |
| **Triazole** | (2R,3R,4S,5R)-2-(3-Ethynyl)-1H-1,2,4-triazol-1-yl-5-(hydroxymethyl)tetrahydofuran-3,4-diol (ETAR) (8a) | Flavivirus | 25 |
| | 3-(5-[4-(Trifluoromethyl)phenyl]-4H-1,2,4-triazol-1-yl)-1H-indole (8b) | TMV | 26 |
| **Oxadiazole** | 5-(4-Amino-3-ethyl-2-thioxo-2,3-dihydrothiazol-5-yl)-1,3,4-oxadiazole-2(3H)-thione (9aa) | FC-CoV, FHV, HSV-1 and HSV-2 | 27 |
| | 5-(4-Amino-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)-1,3,4-oxadiazole-2(3H)-thione (9ab) | Vaccine virus, HCV, EHV-4, BVDV | |
| | 2-[5-(2-Phenythiazolinylidine)]-4,5-dihydro-1,3,4-oxadiazol-2-yl]acetornitrile (9b) | | |
| **Thiadiazole** | 2-Methylsulfanyl-5-(4-methyl-1,2,3-thiazol-5-yl)-1,3-oxadiazole (10aa) | TMV | 28 |
| | Ethylsulfanyl-5-(4-methyl-1,2,3-thiazol-5-yl)-1,3-oxadiazole (10ab) | | |
| | 2-[4-Chlorobenzyl)sulfanyl]-5-(4-methyl-1,2,3-thiazol-5-yl)-1,3-oxadiazole (10ac) | | |
| | 2-Methyl(sulfanyl)-5-(4-methyl-1,2,3-thiazol-5-yl)-1,3-oxadiazole (10b) | | |
| **Pyridine** | 3-Benzy1-3-ethyl-6-methyl-3H-[1,2]oxathiol0-[4,3-]pyridine-1,1-dioxide (11aa) | HV, HCMV, VZV, etc. | 29 |
| | Methyl-3-benzy1-3-ethyl-3H-[1,2]oxathiol0-[4,3-]pyridine-6-carboxylate-1,1-dioxide (11ab) | | |
| | 3-Benzyl-3-ethyl-1H-3H-[1,2]oxathiol0-[4,3-]pyridine-6-carboxylate-1,1-dioxide (11ac) | | |
| | 2-(3-Bromophenyl)-4-[1-(6-chloropyridin-3-yl)methoxyphenyl]-2,3-dihydrobenzol[b][1,4]thiazepine (11b) | TMV | 31 |
| | 4,6-Dimethyl-2-[1(2S,3R,4S,5R,6S,6aR)-3,4-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyrano-2-yl]sulfanyl]nicotinomitrile (11c) | | |
| | 4,6-Dimethyl-2-[1(2S,3R,4S,5R,6S,6aR)-3,4-trihydroxytetrahydro-2H-pyrano-2-yl]sulfanyl]nicotinomitrile (11d) | CV-B4 and HSV-1 | 30 |
| **Pyrimidine** | 5-(5-[sec-Butylsulfanyl]-1,3,4-thiadiazol-2-yl)-2-methylpyrimidin-4-amine (12a) | TMV | 32 |
| | N-[4-[4-[4-(4-Cyano-2,6-dimethylphenoxy)]thieno[3,2-d]pyrimidin-2-yl]aniio]-cyclohexylsulfamoyl]phenyl]acetamide (12ba) | HIV | 33 |
| | 4-Cyano-N-[4-dimethyl-2,6-dimethylphenoxy]thieno[3,2-d]pyrimidin-2-yl]aniio]-cyclohexylbenzenesulfonamide (12bb) | | |
| **Quinazole** | 1-(2-Adamantan-1-yl)-2-tert-butyl-5,6,7,8-tetrahydroquinazolin-4-amine-1-oxide (13a). | TEBV | 34 |
| **Quinaxoline** | Ethyl-4-[1(2,3-dimethoxyquinolin-6-yl)methyl]benzoate (14aa) | CV-B5 | 35 |
| | 4-[1(2,3-Dimethoxyquinolin-6-yl)methyl]benzoic acid (14ab) | | |
| | Ethyl-4-[1(2,3-dimethoxyquinolin-6-yl)methyl]benzol]nicotinate (14ac) | | |
| | Ethyl-2-(6,7-dimethyl-3-oxo-3,4-dihydroquinolin-2-yl)acetate (14b) | HCV | 36 |
| | 6,7-Dimethyl-3-[1(4-(4-Chlorobenzy]yl]phenyl]-5-(pyridin-2-yl)]penta-1,4-dien-3-one O-quinolin-2-yl oxime (14d) | TMV | 37 |
derivatives displayed potent antiviral activity against HSV-1 grown on Vero cells. A variety of indole derivatives were synthesized and tested with the hope to get better antiviral agents. Among the tested derivatives, compounds 1a,b (Fig. 1) showed the highest activity and reduced the number of viral plaques of HSV-1 with respect to aphidicolin as positive control.12

On the other hand, a series of flutimide analogs, specifically novel lipophilic 1,2-annulated indole diketopiperazines were rationally developed. Various substituents such as OH, MeO, Cl, and F were introduced into the core structure. The obtained analogs were evaluated for their inhibitory effect on IAV and HCV RNA replication in the subgenomic replicon assay. Pyrazolo[1,2-α]indole-1,3(2H,4H)-diones 1ca–cd (Fig. 1) following mild and experimentally convenient protocol, offer a promising motif for further construction of new analogs with improved antiviral properties through appropriate substitution in diketopiperazine or indole cycles. Cytotoxicity of compounds was determined toward Huh 5-2 replicon cells and HEK293T cells.13

Isoindole ring is well-used heterocyclic unit in organic chemistry and is naturally occurring in some alkaloids. Isoindole moiety fused with different heterocycles displayed potent antiviral activity against RSV which is a major cause of respiratory tract infections in infants, children, and adults. The antiviral activity was found to be inherent in a single enantiomeric series, and compound 2a, known also as BTA9881, was identified as a candidate for preclinical trials (Fig. 1).14

**Pyrazole, imidazole, imidazopyridine, indazole**

Pyrazole is a ubiquitous motif in biologically active compounds and therefore represents an interesting template for medicinal chemistry. Pyrazole derivatives are the subject of many investigations due to their extensive potential biological activities. Bernardino et al. synthesized and evaluated different pyrazolonaphthyridine derivatives with potential activity against HSV-1. In general, 3H-benzo[h]-pyrazolo[3,4-h]-1,6-naphthyridines were more effective inhibitors than the corresponding 3H-pyrido[2,3-b]pyrazolo[3,4-h]-1,6-naphthyridines. Compounds 3aa–ad (Fig. 2) exhibited the highest antiHSV-1 activity among obtained derivatives. They were tested as inhibitors of HSV replication in Vero cells (obtained from the American type culture collection). Thus, compound 3ad prevented the effect of HSV-1 on Vero cells up to 91% at 50 μM concentration and exhibited low cytotoxicity (CC50 600 μM).15

Similarly, a series of novel pyrazole-fused derivatives had been successfully synthesized through a one-pot two-
step procedure. Their antiviral activity was investigated by Han and coworkers. Thus, compound 3b (Fig. 2) showed the highest antiviral activity against BVDV in Madin–Darby bovine kidney (MDBK) cells and lower cytotoxicity using the MTT method than ribavirin as positive control.16

Luo et al. synthesized a series of novel thiazolyl-benzimidazole derivatives and evaluated their antiviral activity against HBV and cytotoxicity on the HepG2.2.15 cell line. Among the derivatives, compound 4a (Fig. 2) showed good antiviral activity and high selectivity.17

A series of novel 5-nitro-1H-benzimidazole derivatives substituted at N-1 position by heterocyclic systems were synthesized, and their antiviral activity against RVA and HAdV7 was evaluated. Compounds 4b,c (Fig. 2) were the most promising with high antiviral activity in Hep-2 and MA104 cell lines (obtained from VACSERA, Egypt) previously cultured in 96-well multiwell plates (Greiner-Bio One, Germany) to estimate nontoxic doses of the tested samples.18

Imidazopyridine is one of the important fused heterocycles and is recognized as a "drug prejudice" scaffold due to the wide range of its application in medicinal chemistry. A series of novel biphenyl derivatives of imidazo[1,2-α]-pyridine and imidazo[1,2-b]pyridazine were synthesized by Enguehard-Gueiffier et al. using known hit compound Ttou 84 to optimize the inhibitory properties on the replication of the BVDV and HCV by introducing various substituents at different sites of the hit. Thus, compound 5a (Fig. 2) was proved to be the most selective inhibitor of BVDV replication. Pyridazine derivative 5b (Fig. 2) showed antiviral activity in the HCV replicon system.19

Tetrahydroindazoles and their derivatives have attracted attention due to their exclusive pharmacological applications. Indazole derivatives were synthesized by condensation reaction of 4-phenylcyclohexanone with various aldehydes and were employed in antiviral activity tests against CV-B4, HAdV7, and RVA using the plaque assay method. Indazole derivative 6aa exhibited moderate activity against both CV-B4 and RVA and possesses promising activity against HAdV7. Noteworthy, that indazoles 6ab and 6b revealed higher activity against HAdV7 and also revealed promising activity against rotavirus Wa strain (Fig. 2).20

**Thiazole**

Thiazole is an effective nucleus for a wide range of applications as pharmaceutical agents. It was first described by Hantzsch and Weber in 1887.21 Thiazoles occur naturally and are isolated from microbial and marine sources. The scaffold is present in more than 18 FDA-approved drugs and as a part of more than 70 experimental drugs.

A series of C-3,5-disubstituted imidazo[2,1-b]thiazole-6-carbaldehydes was synthesized by Barradas et al. Cytotoxicity was evaluated in Vero cells by MTT method, and antiviral activity was assayed using JUNV strain IV4454 as the model system. The desired products 7aa,ab were obtained by a convergent synthetic pathway from available 6-bromo-6-deoxy-1,2-O-isopropylidene-3-O-methyl-α-D-xylo-hexofuranos-5-ulose. Interestingly, that antiviral activity of the analyzed compounds decreased drastically when the Me group of the carbohydrate residue was replaced by the more polar Ac group. The most active compounds 7aa, 7ab (Fig. 3) showed higher antiviral activity against JUNV in Vero cells than the reference substance ribavirin.22

The synthesis of the compounds based on bisthiazole motif connected to pyrazole or thiazole scaffold with imine linker were reported by Dawood et al. in order to fight HCV virus. The in vitro antiviral screening of the test compound was achieved in USA. Product 7b showed promising activity against HCV virus strain (CON-1, Genotype-1b) and was subjected to further screening (Fig. 3).23

Lozynskyi et al. revealed a convenient protocol for the synthesis of a series of novel thiopyrano[2,3-d]thiazole-6-carbaldehydes via regio- and diastereoselective hetero-Diels–Alder reaction of 5-arylidene-4-thioxo-2-thiazolidinone by the [4+2] cyclization with acrolein. The synthesized compounds were evaluated for antiviral activity according to the antimicrobial acquisition and coordinating facility (AACF) screening program. Compounds 7ca,cb were found to be the most active. Thus, compound 7ca showed the best antiviral activity against EBV in Daudi cell cultures and compound 7cb was the most active against HCV (Fig. 3).24

IAV is extremely disposed to cause periodic epidemics and pandemics in the world through evolution by point mutations or swapping of gene segments, correspondingly. Hu et al. demonstrated antiviral effect of N-(4-nitrophenyl-
methyl)benzothiazol-6-amine (7d), known as N30, against IAV, including oseltamivir- and amantadine-resistant strains. The authors have excluded the target of neuraminidase or hemagglutinin and found that N30's antiviral mechanism may involve the inhibition of guanine nucleotide synthesis by inhibiting the activity of inosine-5'-monophosphate dehydrogenase type II (Fig. 3). 24

Triazole, oxadiazole, thiadiazole

1,2,4-Triazole is an important five-membered heterocycle found in many molecules with significant biological activities. 1β-D-Ribofuranosyl-3-ethynyl[1,2,4]triazole (ETAR) (8a) is a promising broad-spectrum antiviral drug with substantially higher efficacy than ribavirin against flaviviruses via inhibition of the enzyme inosine-5'-monophosphate dehydrogenase (IMPDepH) and has comparable in vitro toxicity (Fig. 4). 25

Zhao et al. designed and synthesized a series of nortopsentin analogs containing 1,2,4-triazole system, which showed good antiviral activities against TMV in vivo (Fig. 4). Compound 8b with higher antiviral activity than nortopsentin D and ribavirin emerged as a new antiviral lead compound. 26

The synthesized 1,3,4-oxadiazole-containing thiazole derivatives 9aa,ab (Fig. 4) were evaluated as cytotoxic and antiviral agents against FCoV, FHV, HSV-1, and HSV-2 which might be also due to the presence of 4-NH2 group in the molecules. Compounds 9aa,ab were obtained from 1,3,4-oxadiazole derivative 2-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetonitrile in presence of ethyl isothiocyanate and 1,3,4-oxadiazole derivative 2-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetonitrile in presence of ethyl isothiocyanate and phenyl isothiocyanate, respectively. Note-worthy, that compound 9b among the analogs was the most effective against vaccinia virus, HSV, CV-B4, and VSV. 27

Modification of substituents of 1,2,3-thiadiazole has little impact on versatility in biological activity. Thus, for example, in 2010, two independent groups presented a series of 4-methyl-1,2,3-thiadiazole-containing 1,2,4-triazoles 29 and 4-methyl-1,2,3-thiadiazole-5-carboxylates, 30 which possessed good antiviral activity. Similarly, Xu et al. few years later generated a number of 1,2,3-thiadiazole derivatives containing thioether and sulfone groups 10aa-ac and 10b which showed potent antiviral activities against TMV. 28

Pyridine, pyrimidine

From the biological interest, the synthesized fused bicyclic systems with various functional groups allow to form new interactions with cellular or viral targets. De Castro et al. described β-amino-γ-sultone as useful intermediate for the synthesis of previously virtually unknown 3H-[1,2]oxathiolo[4,3-b]pyridine 1,1-dioxide bicyclic heterocyclic systems (Fig. 5) and evaluated these novel structures against HIV, HCMV, VZV, and a broad variety of other DNA/RNA viruses. Authors were pleased to found that compounds 11aa-ac inhibited HIV-1-induced cytopathicity. 29

A series of novel 1,5-benzothiazepine derivatives containing pyridine moiety were synthesized and screened for their antiviral activity against TMV in vivo. The corresponding target compounds with different substituents exhibited curative activity against TMV compared to that of Ningnanmycin. Thus, compound 11b was identified as an excellent lead compound with antiviral activity against TMV as well as the most promising candidate for the agricultural use. This research indicated that target compounds may function as potential lead structures for the discovery of new antiviral agents. 31

Thioglycosides, where the anomic carbon of the sugar motif is linked to the proper heterocycle through a thioether bond, were recognized to be of biological interest. Elgemeie et al. worked on the synthesis, antiviral and cytotoxic activities of a number of heterocyclic thioglycosides such as pyridine thioglycosides, pyrimidine thioglycosides, imidazole thioglycosides, pyrazole thioglycosides, triazole thioglycosides, oxadiazole thioglycosides, thiophene thioglycosides, quinoline thioglycosides, thienopyrazole thioglycosides, and pyrazolopyrimidine thioglycosides. Recently, this research team has incorporated the phosphoramidate functionality to pyridine- and pyrimidine-based thioglycosides as sofosbuvir thio analogs. The compounds were prepared by coupling mercapto-derivatized heterocyclic bases with the appropriate α-bromo-O-acetylated sugars and followed by the hydrolysis of the acetate esters under basic conditions that were consequently conjugated with the phosphoramidating reagent to afford the desired thioglycoside protides. The compounds were estimated for their antiviral activities against different viral cell lines: HAdV7, HAV, CV-B4, and HSV-1. Only compounds 11c,d showed notable antiviral activity against CV-B4, reflected from the CC50 values of 17 and 20 μg/100 μl and IC50 values of 4.5 and 6.0 μg/100 μl, respectively. The same two compounds elicited remarkable activities toward HSV-1, represented from the CC50 values of 17 and 16 μg/100 μl and IC50 values of 6.3 and 6.6 μg/100 μl, respectively. Only compound 11d showed a remarkable activity against HCV. 32

2-Substituted 2-methylpyrimidin-5-yl-1,3,4-thiadiazole derivatives (Fig. 5) were synthesized by Wu et al. and evaluated for antiviral activity against TMV in vivo.

Figure 4. Derivatives of triazole, oxadiazole, and thiadiazole.
Notably, both of compounds showed potent antiviral potency against wild-type HIV-1 in MT-4 cells. Among these derivatives, compound \( \text{12a} \) demonstrated the best curative effect, which was better than that of commercial agent Ningnanmycin.\(^{32}\)

Liu et al. designed and synthesized a series of novel thiopheno[3,2-\(d\)]pyrimidines with variety of substituents on cyclohexyl moiety that possibly interact with binding pocket of HIV-1 non-nucleoside reverse transcriptase and evaluated their activity against HIV-1 strains. All the derivatives exhibited moderate to excellent potency against wild-type HIV-1 in MT-4 cells. Among them, compounds \( \text{12ba, bb} \) were effective against most tested mutant strains in MT-4 cells and proved to be active at nanomolar concentration (\( EC_{50} \) 9.2 and 7.1 nM, respectively). Notably, both of compounds showed potent antiviral activity against K103N and E138K strains (Fig. 5).\(^{33}\)

Quinazoline, quinoxaline

Quinazoline and its isomer quinoxaline are bicyclic aromatic heterocycles consisting of two fused cycles – benzene and pyrimidine. A representative series of 4-amino-tetrahydroquinazoline derivatives \( \text{13} \) with aliphatic and aromatic substituents as well as with adamantyl framework (Fig. 6) were investigated in relation of their activity against TBEV reproduction in porcine embryo kidney (PEK) cells. A bulky hydrophobic adamantane fragment was identified to be important for the antiviral activity.\(^{34}\)

Quinoxaline derivatives are an emergent class of heterocyclic compounds with a wide spectrum of biological activities and therapeutic applications. The synthesis of some quinoxaline derivatives and evaluation of their cytotoxic and antiviral activity against different RNA and DNA viruses is a hot research topic. Enteroviruses CV-B4 and CV-B5 infections have a worldwide distribution and cause many harmful diseases. CV-B5 is associated with encephalitis and myocarditis in immunocompromised children and central nervous system disease in the elderly adults. Three compounds \( \text{14aa–ac} \) showed very potent and selective antiviral activity against CV-B5 and cytotoxicity against different cell lines (MT-4, MDBK, BHK, and Vero-76). In addition compound \( \text{14aa} \) inhibits the penetration possibly targeting the viral capsid protein VP1.\(^{35}\)

Different quinoxalin-2-one derivatives were synthesized via different nucleophilic reactions. Synthesized compounds were tested for antiviral activity against HCV, HBV, and HSV-1. Simultaneously their safety profile as well as selectivity against viral strains were investigated. Thus, two of the test compounds, namely, quinoxalin-2-ones \( \text{14b,c} \) showed potent activity and selectivity against HCV compared to that of ganciclovir as well as exhibited low cytotoxicity index against cell viability.\(^{36}\)

A series of penta-1,4-dien-3-one oxime ethers containing quinoxaline moiety were synthesized and their antiviral activity was evaluated against TMV. Compound \( \text{14d} \) showed remarkable curative, protective, and inactivation activity against TMV. The antiviral activity of this compound was evaluated by the half-leaf method using the commercial agent Ningnanmycin in the control experiment.\(^{37}\)
This review points out a growing interest in the development of heterocyclic compounds and their applications in antiviral treatment. Highly potent and specific antiviral drugs are now available for treatment of different types of viruses. The emergence of viral resistance demands new chemical scaffolds in selective treatment. Many scientific groups turn their attention to heterocycle-containing therapeutic agents that may emerge effective against virus strains. Future research will be focused on the chemical functionalization of some heterocyclic moieties to improve their inhibitory activity and make them a great antiviral platform giving a direct impact on the environment and society.

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