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Antiviral agents – benzazine derivatives

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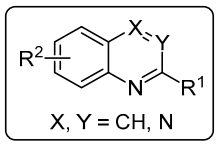


Antiviral activity against:
- human immunodeficiency virus
- influenza virus
- herpes viruses
- hepatitis B virus
- enteroviruses

The review outlines the results of studies of the antiviral activity of quinoline, quinoxaline, and quinazoline derivatives published over the past 5 years. The supplied data indicate the enormous potential of benzazines for the design of effective antiviral drugs.

Keywords: benzazines, quinazoline, quinoline, quinoxaline, antiviral activity.

Of the vast number of pathogens of infectious diseases, a special place belongs to viruses. It is no coincidence that the World Health Organization has declared the 21st century the century of viruses. Over the past 20 years, the world has faced epidemics of coronavirus infection: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19; outbreaks of avian and swine flu; the spread of Ebola and Zika fever, which have become serious challenges to all of humanity.

Slowly progressing, persistent, and latent viral infections, the mortality rate from which exceeds the mortality rate from acute infections, pose no less danger. Some pathogens (for example, HIV) are characterized by long latency periods, high antigenic variability, and the ability to affect the immune system up to its complete destruction. Other viruses (for example, human herpesvirus 7 (HHV-7) and cytomegalovirus) may not explicitly manifest themselves but become activated due to stress or other factors and, by suppressing the immune system, "open the gate" for more dangerous viruses. In this regard, research and development of new effective antiviral drugs is a priority task of medicinal chemistry.

Benzazines are heterocycles of great potential which, due to their interaction with various molecular targets, can serve as the most important scaffold for the development of effective therapeutic drugs, including those for antiviral therapy. This is evidenced by regularly published reviews on the biological activity of quinolines, quinoxalines, and quinazolines, which, as a rule, are devoted to a specific class of compounds and the discussion of various types of biological activity. At the same time, no separate review articles on the antiviral activity of benzazines can be found.

Promising directions for the use of quinoline derivatives are outlined in a review by Goncharuk et al.[1] published in 2018. The discussion of antiviral activity is limited by data on compounds effective against Japanese encephalitis virus and HIV.

Quinoxaline derivatives are the subject of increased interest from researchers due to the wide spectrum of their biological activity. A 2015 review by Pereira et al.[2] noted the ability of quinoxalines to inhibit the replication of herpes simplex viruses of types 1 and 2 (HSV-1 and HSV-2), cytomegalovirus, varicella zoster and shingles viruses. Among the quinoxalines, potent inhibitors of HIV-1 reverse transcriptase activity and HIV-1 replication in tissue cultures have been identified. Quinoxalines, the target of which is the NS1 protein of influenza virus which plays a central role in suppressing the host cell interferon response, facilitation of the replication, and spread of the virus, are especially represented. Tariq et al.[3] provided data on the antiHIV activity of quinoxaline derivatives as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and HIV integrase inhibitors as part of a review of the antiviral properties of quinoxalines published in 2018.

In the review by Khan et al. from 2015[4] devoted to derivatives of quinazolines and quinazolinones, there is no separate section on antiviral agents; only 3-substituted 2-phenylquinazolines with antiviral activity are discussed.

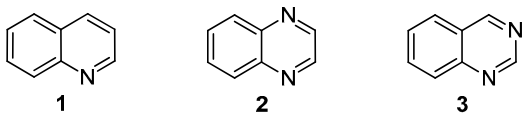


Figure 1. The structures of quinoline (**1**), quinoxaline (**2**), quinazoline (**3**).

The review published in 2018 by Alagarsamy et al.[5] contains a section on the antiviral activity of quinazolines which supplies data on derivatives active against HIV-1 and HIV-2, cytomegalovirus, adenovirus type 2, HSV-1, tobacco mosaic virus, vaccinia virus; only a few compounds with moderate activity against influenza virus were reported.

The purpose of this minireview is to update the data on the antiviral activity of benzazine derivatives of quinoline (**1**), quinoxaline (**2**), and quinazoline (**3**) (Fig. 1), consider potential molecular targets of benzazine antiviral agents, and analyze the structure–activity relationship according to data published in 2015–2020.

Quinolines exhibiting antiviral activity

Compounds that are active against HIV-1 have been identified among quinoline derivatives. The main targets of potential antiHIV drugs are viral proteins involved in the intracellular multiplication of HIV (reverse transcriptase, integrase, and protease), as well as viral and cellular proteins involved in the attachment of viral particles to the cell. Thus, bromine- and chlorine-substituted chalcones **4a**–**e** (Fig. 2) exhibited a high degree of inhibition of HIV reverse transcriptase.[6]

Testing of 8-(naphthalen-1-yl)-substituted quinolines **5**–**8** (Fig. 3) revealed promising inhibitors of HIV-1 ribonuclease H (RNase H) (Table 1). *In vitro* studies showed that 7-isopropoxy-8-(naphthalen-1-yl)quinoline (**5**) acts in the early stages of viral replication prior to viral assembly and budding. Compound **5** inhibits the activity of RNase H and binds directly to HIV-1 reverse transcriptase. In addition, additive inhibitory activity against pseudotyped viruses has been noted when quinoline **5** is competitively dosed with the clinically used non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz. When tested against an NNRTI-resistant HIV-1 isolate, compound **5** showed a 5.1-fold decrease in the half-maximal inhibitory concentration (IC_{50}) while the activity of the reference drug efavirenz decreased by 7.6. These results indicate that quinoline **5** is a potential lead compound in the development of new HIV-1 RNase H inhibitors.[7]

A wide range of quinoline derivatives **9**–**11** (Fig. 4) have been studied as novel inhibitors of HIV penetration.[8]

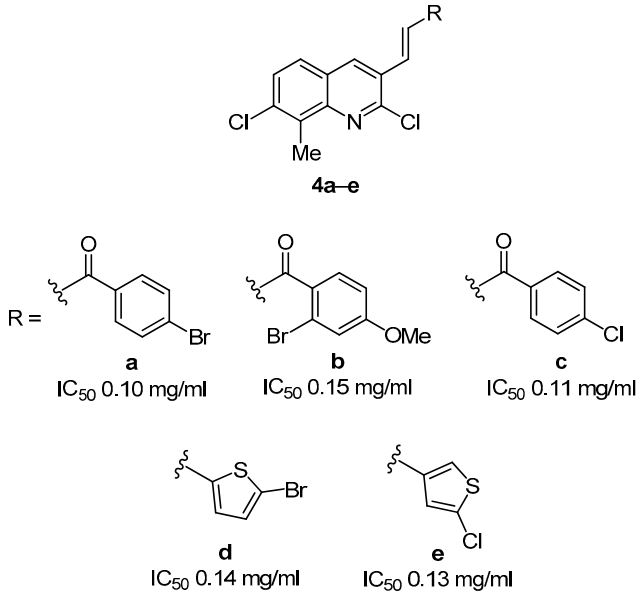


Figure 2. The structures of quinoline derivatives **4a**–**e** and their half-maximal inhibitory concentration (IC_{50}) in regards to HIV reverse transcriptase (IC_{50} 0.23 mg/ml for antiHIV drug nevirapine).

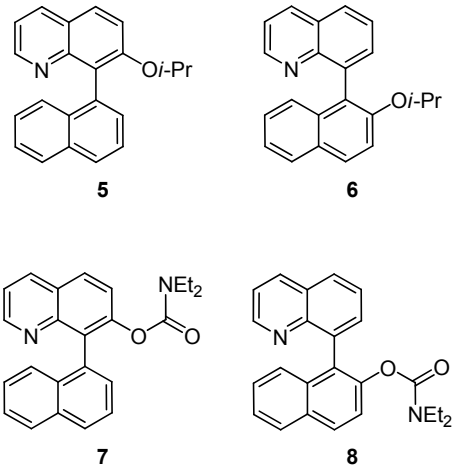


Figure 3. The structures of quinoline derivatives **5**–**8**.

Table 1. Activity, cytotoxicity, and selectivity of 8-(naphthalen-1-yl)-substituted quinolines **5**–**8** against HIV-1 in the TZM-b1 cell line*

Compound	IC_{50}, μM		CC_{50}, μM		SI
	Strain HXB2	Strain YU2	Strain 89.6	Cell line TZM-bl	
5	6.7 ± 0.9	8.9 ± 0.6	4.7 ± 1.6	68.5 ± 17.1	14.6
6	>100	>100	>100	>100	–
7	61.4 ± 3.3	77.6 ± 10.8	56.6 ± 0.8	95.0 ± 13.1	1.7
8	12.6 ± 1.6	14.0 ± 0.8	16.8 ± 3.0	69.3 ± 4.9	5.5
Efavirenz	0.0009 ± 0.0002	0.0023 ± 0.0003	–	Not effect	–

* IC_{50} – half-maximal inhibitory concentration, CC_{50} – half-maximal cytotoxic concentration, SI – selectivity index (CC_{50}/IC_{50}).

Compound **10a** (Fig. 5) showed the highest *in vitro* activity against HIV-1 strains HIV-1VB59 and HIV-1UG070 in TZM-bl cell lines (IC_{50} 3.35 ± 0.87 and 2.57 ± 0.71 μM, respectively). Its ability to inhibit entry into the target cell (IC_{50} 1.40 ± 0.28 μM, therapeutic index

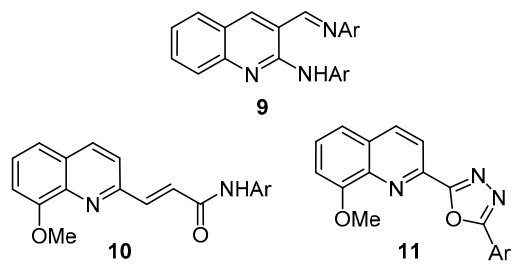


Figure 4. The structures of quinoline derivatives **9**–**11**.

(TI) 38.29) as well as the process of fusion with the target cell (IC_{50} 0.96 ± 0.28 μM, TI 55.83) is given as the purported mechanisms of action.[8]

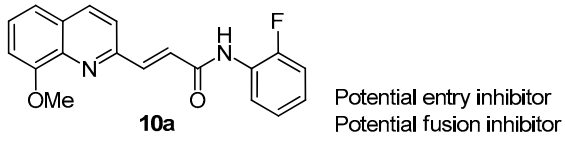


Figure 5. The structure of quinoline derivative **10a**, a potential HIV inhibitor.

Of a number of synthesized 6-(1,2,3-triazol-1-yl)-substituted quinolones, compounds **12a**,**b** (Fig. 6) were identified that are capable of inhibiting the activity of the neuraminidase of wild-type influenza virus (WT). It was noted that a change in the position of the 1,2,3-triazole fragment as well as a decrease in the size of the R substituent lead to the loss of anti-influenza activity, probably because of disruption of the patterns of interaction with targets.[9]

Compounds **12a**,**b** at a concentration of 50 μM most effectively inhibited neuraminidase of influenza virus H3N2 by 89.0 and 94.8%, respectively. For comparison, oseltamivir (OST) at the same concentration inhibited neuraminidase activity by 100%. A study of the efficacy of compound **12b** against circulating WT and OST-resistant influenza A and B strains showed that quinolone **12b** has some advantages over OST. Although OST was more effective against wild strains, the IC_{50} values for compound **12b** did not change significantly in the presence of OST resistance mutations. Thus, the ratio of IC_{50} of OST-resistant strains to IC_{50} of WT strains in the case of compound **12b** was 0.13, 3.0, and 1.4 for influenza virus strains A (H3N2), A (H1N1), and B, respectively. Similar IC_{50} ratios for OST increased to 27, 380, and 5.3, respectively[9] (Table 2). These results show that (1,2,3-

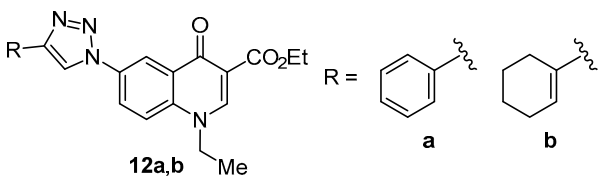


Figure 6. The structures of quinoline derivatives **12a**,**b**.

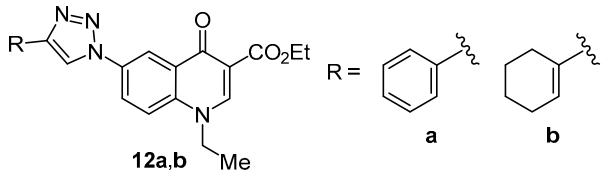


Figure 6. The structures of quinoline derivatives **12a**,**b**.

Table 2. Efficiency of inhibition of WT and OST-resistant influenza strains by compound **12b** and the comparison drug OST

Influenza strain	IC_{50}		Ratio IC_{50} (OST-resistant strain) / IC_{50} (WT strain)	
	12b, μM	OST, nM	**12b**	OST
A/H3N2 WT	19.90 ± 1.3	0.15 ± 0.032		
A/H3N2 E119V	2.60 ± 0.8	4.19 ± 0.16	0.13	27.0
A/H1N1 WT	3.50 ± 0.9	0.21 ± 0.011		
A/H1N1 H275Y	10.60 ± 0.9	79.94 ± 3.2	3.00	380.0
B WT	22.00 ± 1.1	16.00 ± 2.9		
B R152 K	30.00 ± 1.6	85.00 ± 5.4	1.40	5.30

triazol-1-yl)-substituted quinolines may be of interest for the development of new anti-influenza drugs against OST-resistant virus strains.

In recent years, data have appeared on the ability of quinoline derivatives **13**–**15** to inhibit the replication of arboviruses such as Zika (ZIKV) and chikungunya (CHIKV).[10] 2,8-Bis(trifluoromethyl)quinoline derivatives **13a** and **14** (Fig. 7, Table 3) showed the highest antiZIKV activity (half-maximal inhibitory concentration (EC_{50})

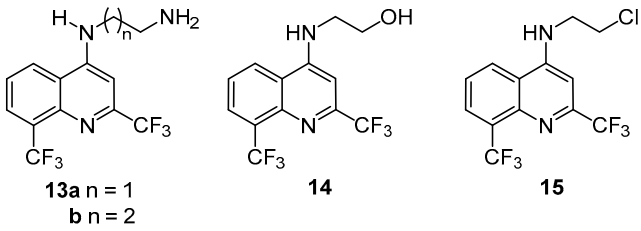


Figure 7. The structures of quinoline derivatives **13**–**15**.

Table 3. Activity, cytotoxicity, and selectivity of 2,8-bis(trifluoromethyl)quinolines **13**–**15** in respect to replication of ZIKV in the Vero cell line*

Compound	EC_{50}, μM	CC_{50}, μM	SI
13a	0.8 ± 0.06	195 ± 8.9	243
13b	2.0 ± 0.1	287 ± 21	143
14	0.8 ± 0.03	189 ± 10	236
15	1.4 ± 0.09	316 ± 27	225
Mefloquine	3.6 ± 0.3	212 ± 14	58

* EC_{50} – half-maximal effective concentration, SI – selectivity index (CC_{50}/IC_{50}).

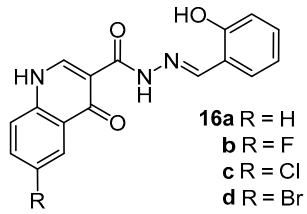


Figure 8. The structures of quinoline derivatives **16a**–**d**.

Table 4. Cytotoxicity, activity, and selectivity of compounds **16a**–**d** against ZIKV and CHIKV in the Vero cell line

Compound	CC_{50}, μM	ZIKV		CHIKV	
		EC_{50}, μM	SI	EC_{50}, μM	SI
16a	502 ± 4.38	0.76 ± 0.028	660.9	2.85 ± 0.12	176.2
16b	669 ± 4.33	0.75 ± 0.011	892.9	1.06 ± 0.077	631.7
16c	1113 ± 6.11	0.79 ± 0.005	1409.7	2.77 ± 0.18	402
16d	443 ± 5.1	0.81 ± 0.009	547.5	2.7 ± 0.13	164.2
Ribavirin	297 ± 4.95	3.95 ± 0.095	75.2	2.42 ± 0.49	122

0.8 μM), which is 5 times more effective than mefloquine, an antiviral drug approved by the Food and Drug Administration (FDA).[10a]

A study[10b] reported that *N*'-(2-hydroxybenzylidene)-4-oxo-1,4-dihydroquinoline-3-carbohydrazides **16a**–**d** (Fig. 8) showed significant activity in the micromolar concentration range against ZIKV and CHIKV compared to ribavirin. *N*-Acylhydrazones **16a**–**d** were nontoxic toward Vero cells, compounds **16c**,**b** showed the best selectivity (selectivity index (SI) 1409.7 and 631.7 toward ZIKV and CHIKV, respectively) (Table 4).

The synthesized compounds **16a**–**d** were found to have antiviral activity both in the early and post-infectious stages of the action of ZIKV and CHIKV which makes them excellent candidates for the development of antiZIKV and antiCHIKV drugs.[10b]

Phenotypic screening of 7000 compounds using BHK-21 cells infected with dengue virus type 2 (DENV-2) revealed quinolones capable of inhibiting DENV-2 replication. For the lead compounds **17** and **18** (Fig. 9), the EC_{50} for the DENV-2 is 3.9 and 9.2 μM, respectively;[11] however, the antiviral mechanism of action of these compounds is not entirely clear and requires further research.

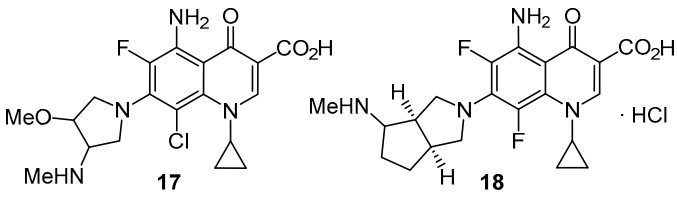


Figure 9. The structures of fluoroquinolones **17** and **18**.

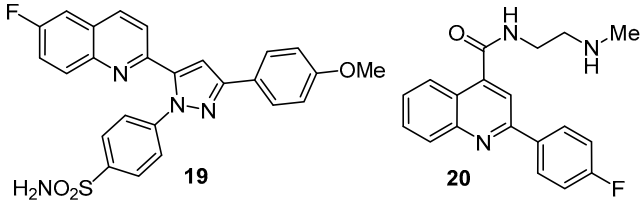


Figure 10. The structures of quinoline derivatives **19** and **20**.

Table 5. Cytotoxicity, activity, and selectivity of compound **20** against non-polyomyelitis enteroviruses EV-A71, EV-D68, and CVB3 in the RD cell line

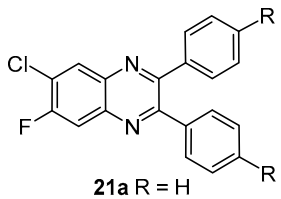
Strain	CC_{50}, μM	EC_{50}, μM	SI
EV-A71	32.4 ± 4.1		
Taiwan, Tainan		31 ± 1.0	10
USA, Alaska		3.6 ± 0.2	9
EV-D68	32.4 ± 4.1		
USA, Kentucky/14-18953		0.2 ± 0.1	162
USA, Missouri/14-18947		0.1 ± 0.02	324
CVB3	40.1 ± 13.2	0.2 ± 0.2	200

Diarylpyrazolyl-substituted quinoline **19** (Fig. 10), which exhibited higher inhibitory activity against DENV-2 (IC_{50} 0.81 μM, SI >246.91), compared with ribavirin (IC_{50} 12.61 μM, SI 4.47) was considered[12] as a potential antiviral drug against DENV. It was shown that compound **19** also effectively inhibits other serotypes of DENV, reduces the clinical manifestations of the disease and mortality in mice infected with DENV.

The quinoline skeleton is currently considered as the basis for the development of effective antiviral drugs for the prevention and treatment of non-polyomyelitis enterovirus infection. As a result of the search for drugs with direct action on the conservative multifunctional viral protein C2 involved in membrane rearrangement, viral assembly, and viral RNA replication, compound **20** was identified (Fig. 10) demonstrating high broad-spectrum antiviral activity against 5 tested strains of non-polyomyelitis enteroviruses (two EV-D68 strains (USA, Kentucky and USA, Missouri), two EV-A71 strains (Taiwan, Tainan and USA, Alaska), and one CVB3 strain), and also showed high microsomal stability with a half-life of 114.7 min[13] (Table 5). Research of this kind is a step forward in the development of sought-after antiviral drugs against non-polyomyelitis enteroviruses.

Quinoxalines exhibiting antiviral activity

Potential inhibitors of HIV-1 integrase were designed and then synthesized based on a created pharmacophore model and 3D analysis of quantitative structure–activity relationship (3D-QSAR). 2,3-Diaryl-substituted quinoxalines **21a**,**b** (Fig. 11) showed the best antiHIV activity and low toxicity (Table 6). It was noted that lipophilic and bulky substituents at positions 2 and 3 of the quinoxaline fragment increase the activity of compounds **21a**,**b** against HIV as compared to unsubstituted quinoxalines or quinoxalines with less bulky substituents.[14]



21a R = H
b R = F

Figure 11. The structures of quinoxaline derivatives **21a**,**b**.

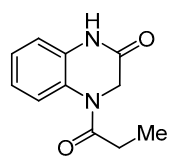
Table 6. AntiHIV activity and cytotoxicity of compounds **21a**,**b** in the cell lines MT-4 and Vero

Compound	Strain IIIB HIV-1 in MT-4 cells			Vero
	IC_{50}, mg/ml	CC_{50}, mg/ml	Protection from HIV, %	CC_{50}, mg/ml
21a	>11.78	11.78	3	>100
21b	>15.45	15.45	3	>100
Nevirapine	0.075	4.00	–	>100
Zidovudine	0.002	2.00	–	–
Lamivudine	0.58	20.00	–	–
Didanosine	17.95	50.00	–	–
Paclitaxel	–	–	–	>100

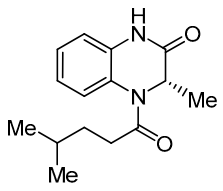
Virtual library screening, molecular docking, and 3D-QSAR study allowed the structure to be optimized followed by synthesis of quinoxalines **22** and **23** (Fig. 12) which showed high antiviral activity against wild and mutant (K103N) HIV reverse transcriptase. Compound **22** showed higher EC_{50} and SI values compared to the commercial drug nevirapine.[15]

Quinoxalines **24a**,**b** and **25a**,**b** were identified to have low toxicity and high activity in the micromolar concentration range (0.06–3.8 μM) against Coxsackie B5 (CV-B5) enterovirus (Fig. 13). It is assumed that the mechanism of action of the obtained compounds is similar to that of the group of rhinovirus inhibitors (pleconaril and vapendavir), namely, inhibition of the VP1 virus capsid protein and preventing its attachment to the host cell.[16]

The structure–activity analysis shows that for the selective activity to be manifested, the carboxyl group in compounds **24a**,**b** and **25a**,**b** must be located in the *para* position of the benzene or pyridyl fragment with respect to

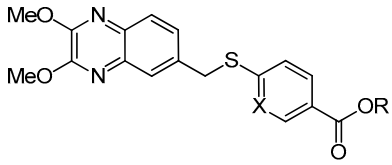


22
EC_{50} 3.1 (1.5–6.2) nM
CC_{50} 98576 (25435–382061) nM
SI 31798



23
EC_{50} 1576 (931–2667) nM
CC_{50} 116818 (94390–144575) nM
SI 74

Figure 12. Structures of quinoxaline derivatives **22** and **23** and their activity, cytotoxicity, and selectivity for HIV in the MT-2 cell line (for nevirapine EC_{50} 6.7 (4.0–11.3) nM, CC_{50} 96171 (154165–170754) nM, SI 14353). The EC_{50} and CC_{50} values are indicated as mean values, the range of values with a confidence level of 95% is indicated in parentheses.



24a X = CH, R = H (EC_{50} 0.09 ± 0.01 μM, SI >1111)
b X = N, R = Et (EC_{50} 0.06 ± 0.01 μM, SI 1083)
25a X = CH, R = H (EC_{50} 0.3 ± 0.05 μM, SI >333)
b X = N, R = Et (EC_{50} 3.8 ± 0.5 μM, SI 23)

Figure 13. The structure of quinoxaline derivatives **24a**,**b** and **25a**,**b**, their activity and selectivity against the CV-B5 in the Vero cell line (for pleconaril EC_{50} 0.005 ± 0.001 μM).

the sulfanyl group. Compound **24a** which showed the highest activity against the CV-B5 virus (EC_{50} 0.09 ± 0.01 μM) was chosen as the lead compound.[16] Given the high activity in combination with low cytotoxicity, quinolines **24a**,**b** and **25a**,**b** can serve as the basis for the development of new drugs for treatment of infections caused by enteroviruses.

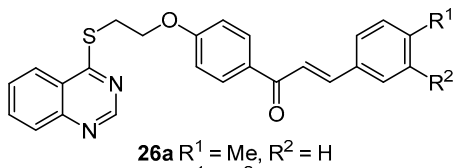
Quinazolines exhibiting antiviral activity

Data on 4-substituted quinazolines with antiviral activity are limited to isolated examples. 2-Sulfanylquinazolines **26a**,**b** containing the chalcone fragment (Fig. 14) (EC_{50} 156.4 and 138.1 μg/ml, respectively) are superior to ribavirin (EC_{50} 436.0 μg/ml) in activity against tobacco mosaic virus.[17]

A number of 4-arylaminoquinazolines **27a**–**d** effectively suppress the replication of human cytomegalovirus.[18] Conjugates **28a**,**b** and **29a**,**b** of 4-arylaminoquinazolines with the sesquiterpene lactone artemisinin were synthesized (Fig. 15) exhibiting antimalarial action. It was shown that derivatives **28a**,**b** and **29a**,**b** are superior in anti-cytomegalovirus activity to ganciclovir.[18b]

The antiviral activity of 2-substituted quinazolinones **30** obtained by cycloaddition of *C*-(diethoxyphosphoryl)-*N*-methylnitrone **31** to 3-substituted 2-vinylquinazolin-(3*H*)-ones **32** in regards to a wide range of DNA and RNA viruses was studied. Several derivatives were active against two types of varicella zoster virus (TK^+ and TK^-) with EC_{50} values of 5.4–13.6 μM, as well as against human cytomegalovirus (EC_{50} 8.94–13.2 μM)[19] (Table 7).

3-Aryl- and 3-benzyl-substituted compounds **30b**–**i** are superior in activity against the TK^- (07-1) strain of varicella zoster virus compared to reference drugs acyclovir and brivudine (EC_{50} 39.2 and 31.9 μM,



26a R^1 = Me, R^2 = H
b R^1 = R^2 = OMe

Figure 14. The structures of quinazoline derivatives **26a**,**b**.

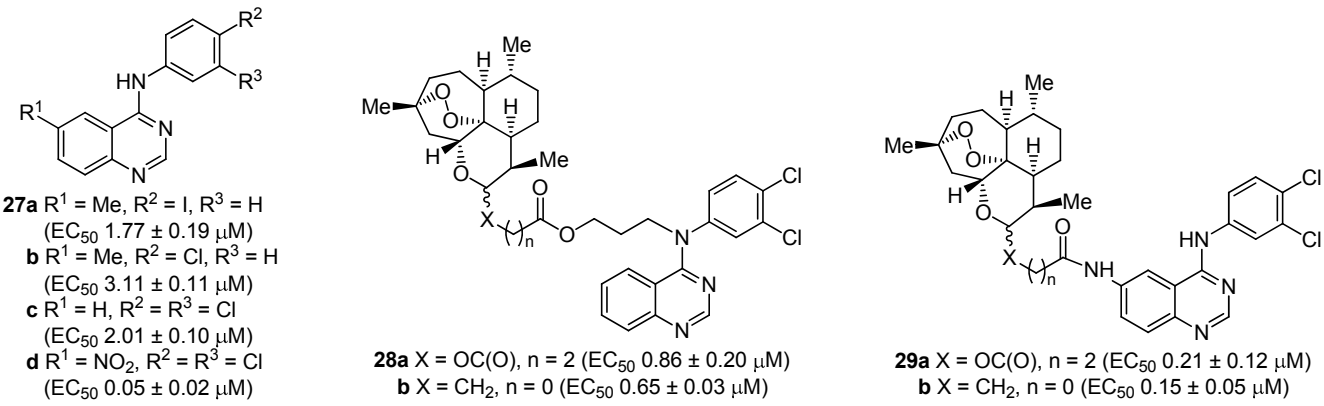
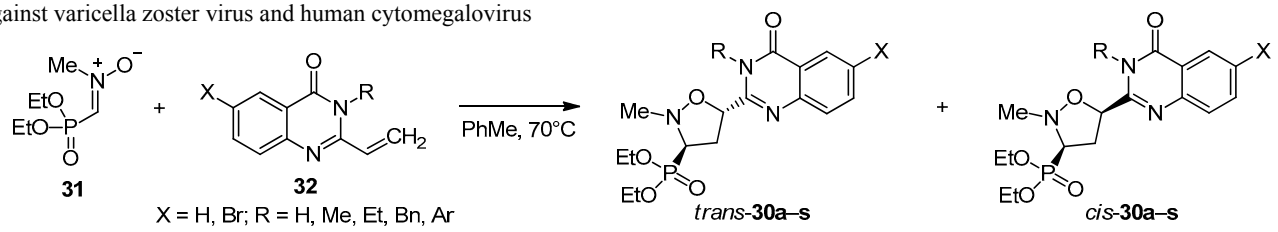


Figure 15. Structures of quinazoline derivatives **27**–**29** and their activity against human cytomegalovirus (laboratory strain AD169-GFP) (for ganciclovir, EC_{50} 2.60 ± 0.50 μM).

respectively); in this case, activation by a viral enzyme is required. At the same time, the activity of quinazolinones **30b**–**i** against the TK^+ (OKA) strain was found to be 360–587 times lower than that of the above reference drugs.[19] It was noted that 6-bromo-substituted 2-isoxazolidinylquinazolin-4(3*H*)-ones are superior in activity to analogs without

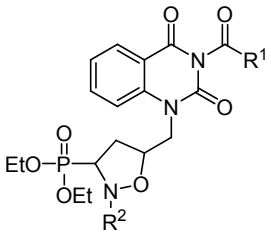
Table 7. Activity of 2-isoxazolidinyl-substituted quinazolin-4(3*H*)-ones **30a**–**s** against varicella zoster virus and human cytomegalovirus



Compound	X	R	EC_{50}, μM		EC_{50}, μM	
			Varicella zoster virus		Human cytomegalovirus	
			TK^+ strain (OKA)	TK^- strain (07-1)	AD-169 strain	Davis strain
cis-**30a**	Br	H	>100	>100	>100	100
trans-**30a**	Br	H	>100	66.87	>100	>100
trans-**30b**	Br	Bn	13.5 ± 7.1	13.6 ± 9.1	20	20
trans-**30c**	Br	2-$O_2NC_6H_4CH_2$	10.3 ± 1.1	5.4 ± 1.0	>20	15.29
trans-**30d**	Br	3-$O_2NC_6H_4CH_2$	8.3 ± 1.4	5.8 ± 1.4	10.4 ± 0.8	11.6 ± 2.5
trans-**30e**	Br	4-$O_2NC_6H_4CH_2$	6.84	7.51	>20	>20
trans-**30f**:*cis*-**30f**, 95:5	Br	2-$FC_6H_4CH_2$	7.76	9.56	8.94	8.94
trans-**30g**	Br	3-$FC_6H_4CH_2$	11.6 ± 5.3	7.7 ± 6.2	10.5 ± 2.2	8.94 ± 0
trans-**30h**	Br	4-$FC_6H_4CH_2$	12.6 ± 2.6	7.5 ± 5.4	12.5 ± 3.9	13.2 ± 3.1
trans-**30i**:*cis*-**30i**, 92:8	Br	2,4-$F_2C_6H_3CH_2$	8.7 ± 3.2	10.5 ± 0.3	9.4 ± 0.46	9.7 ± 1.1
trans-**30j**	Br	Me	>4	>4	>20	>100
trans-**30k**	Br	Et	>20	>20	>20	44.72
trans-**30l**	H	2-$O_2NC_6H_4CH_2$	46.47	100	>100	44.72
trans-**30m**:*cis*-**30m**, 9:1	H	4-$O_2NC_6H_4CH_2$	34.20	42.87	44.72	20
trans-**30n**:*cis*-**30n**, 9:1	H	2-$FC_6H_4CH_2$	6.84	>10		
trans-**30o**	H	4-$FC_6H_4CH_2$	15.29	>20		
trans-**30p**:*cis*-**30p**, 97:3	H	2,4-$F_2C_6H_3CH_2$	9.44	>20		
trans-**30q**	H	Et	38.80	41.57		
trans-**30r**:*cis*-**30r**, 9:1	H	Bn			44.72	>20
trans-**30s**	H	3-$FC_6H_4CH_2$			>100	27.59
Acyclovir			1.55 ± 1.0	39.2 ± 3.6		
Ganciclovir					16.9 ± 6.9	7.7 ± 0.9
Brivudine			0.023 ± 0.008	31.9 ± 16.1		
Cidofovir					1.5 ± 0.2	1.7 ± 0.4

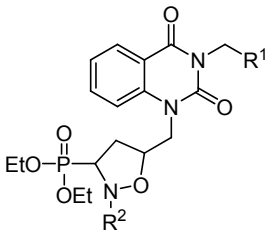
a substituent in the benzene ring.[20] Compounds **30d**,**f–i** are comparable in activity against AD-169 and Davis strains of human cytomegalovirus (EC_{50} 8.94–13.2 μM) to ganciclovir (EC_{50} 16.9 and 7.7 μM) but inferior to cidofovir (EC_{50} 1.5 and 1.7 μM)[19] (Table 7).

Based on 1-allylquinazoline-2,4-diones containing substituted benzoyl or benzyl groups at position 3, isoxazolidine derivatives **33** and **34** were obtained (Fig. 16) which showed high activity against varicella zoster virus and human cytomegalovirus.[21]



33

Varicella zoster virus (TK^+, TK^-): EC_{50} 6.0–21.4 μM



34

Varicella zoster virus (TK^+, TK^-): EC_{50} 3.0–27.1 μM

Human cytomegalovirus: EC_{50} 3.0–13.1 μM

R^1 = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4; R^2 = Me, Bn

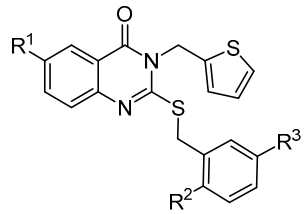
Figure 16. Structures of quinazoline derivatives **33** and **34** and their activity against varicella zoster virus and human cytomegalovirus.

It was found that derivatives of 6-iodo-3-(3-trifluoromethylphenyl)quinazolin-4(3*H*)-ones containing thiosemicarbazone, pyrazole, or azomethine fragments in position 2 have weak or moderate activity against H5N1 influenza virus and are inferior to the reference drug zanamivir.[22]

A wide range of 2-benzylsulfanyl-3-(thiophen-2-ylmethyl)quinazolin-4(3*H*)-ones were studied, and it was shown that compounds **35a–c** (Fig. 17) are the most promising for the development of non-nucleoside drugs on their basis for the treatment of hepatitis B[23] (Table 8).

3-Hydroxy-6-(1,2,3-triazolyl)quinazoline-2,4(1*H*,3*H*)-diones **36a**,**b** (Fig. 18) were obtained by copper(I)-catalyzed 1,3-dipolar cycloaddition of an alkyne to an azide. (4-Nitrophenyl)-substituted derivative **36a** outperforms cidofovir in activity against vaccinia virus 15 times, while 4-methoxy derivative **36b** outperforms the reference drugs against type 2 adenovirus.[24]

Quinazolines which are promising for the development of anti-influenza agents were reported[25] for the first time. Such heterocycles were obtained as bioisosteres of indoles with activity against influenza A virus. The structure–



35a R^1 = H, R^2 = OMe, R^3 = C(O)Me

b R^1 = $OCH_2CH_2NMe_2$, R^2 = R^3 = H

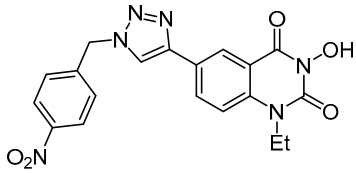
c R^1 = $OCH_2CH_2NEt_2$, R^2 = R^3 = H

Figure 17. The structures of quinazoline derivatives **35a–c**.

Table 8. Cytotoxicity, activity, and selectivity of quinazoline derivatives **35a–c** in relation to hepatitis B virus in the HepG2 cell line

Compound	Testing in lamivudine-sensitive HepG2 2.2.15 cells			Testing of lamivudine- and entecavir-resistant hepatitis B virus strain		
	CC_{50}, mM	DNA replication		CC_{50}, mM	DNA replication	
		IC_{50}, mM	SI		IC_{50}, mM	SI
35a	71.51	4.07	17.57			
35b	21.13	1.54	13.72	26.72	1.90	14.06
35c	15.79	0.71	22.24	17.98	0.84	21.40
Lamivudine	>100	<0.1	>1000	>100	>100	<1

activity relationship against influenza A/WSN/33 (H1N1) virus was analyzed for 2-(quinazolin-4-yl)oxy-*N*-arylacetamides and *N*-[(quinazolin-4-yl)oxyethyl]arylamides,

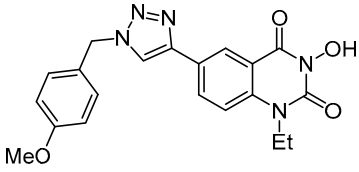


36a

Vaccinia virus EC_{50} 1.7 μM, SI >58.8

Brivudine: EC_{50} 15 μM, SI >16.6

Cidofovir: EC_{50} 25 μM, SI >10



36b

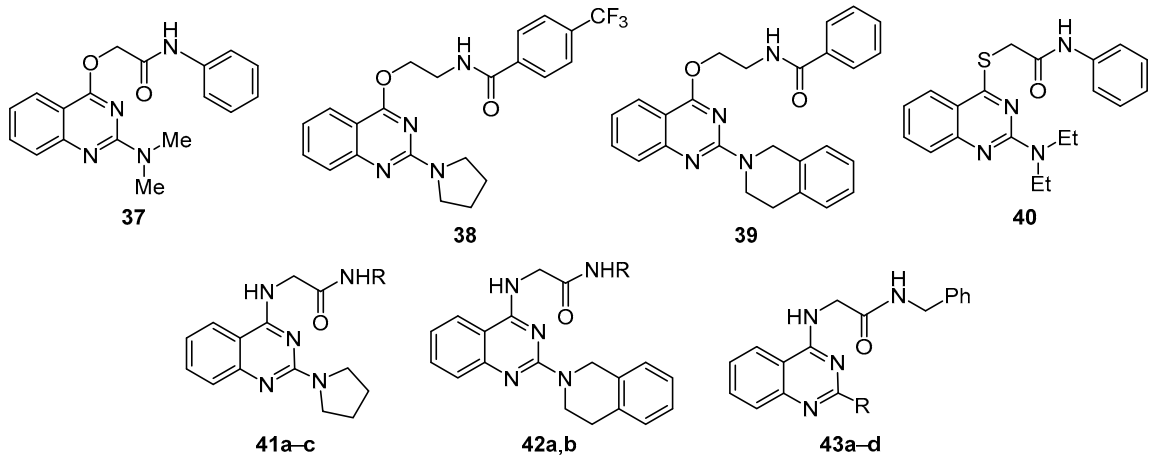
Adenovirus type 2 EC_{50} 6.2 μM, SI >16.1

Cidofovir: EC_{50} 10 μM, SI >25

Zalcitabine: EC_{50} 7.2 μM, SI >34.7

Alovudine: EC_{50} 10 μM, SI >25

Figure 18. Structures of 3-hydroxy-6-(1,2,3-triazolyl)quinazoline-2,4(1*H*,3*H*)-diones **36a**,**b** and their activity and selectivity against vaccinia virus (comparison drugs brivudine and cidofovir) and adenovirus type 2 (comparison drugs cidofovir, zalcitabine, and alovudine).



41a R = Ph, **b** R = naphthalen-2-yl, **c** R = 3,5-$Cl_2C_6H_3$; **42a** R = Ph, **b** R = naphthalen-2-yl
43a R = 1,2,3,4-tetrahydroisoquinolin-2-yl, **b** R = morpholin-4-yl, **c** R = NEt_2, **d** R = 4-methylpiperazin-1-yl

Figure 19. The structures of quinazoline derivatives **37**–**43**.

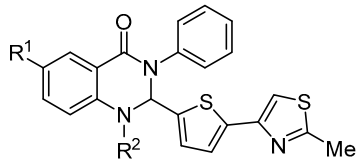
Table 9. Activity, cytotoxicity, and selectivity of 2,4-disubstituted quinazolines **37**–**43** in relation to influenza A/WSN/33 (H1N1) virus in the cell line HEK293T-Gluc

Compound	IC_{50}, μM	CC_{50}, μM	SI
37	3.70 ± 0.82	> 100	>27.03
38	8.64 ± 1.76	> 100	>11.57
39	4.19 ± 0.43	> 100	>23.87
40	7.18 ± 1.89	> 100	>13.93
41a	1.88 ± 0.10	23.28 ± 2.91	12.38
41b	1.29 ± 0.01	59.94 ± 3.04	46.46
41c	9.04 ± 0.57	15.86 ± 0.58	1.75
42a	3.88 ± 0.47	36.64 ± 2.24	9.44
42b	3.43 ± 0.54	> 100	>29.15
43a	6.84 ± 0.68	29.43 ± 0.95	4.30
43b	3.83 ± 0.15	> 100	>26.11
43c	5.00 ± 1.37	> 100	>20.00
43d	11.47 ± 0.54	> 100	>8.72
Ribavirin	15.36 ± 0.93	> 100	>6.51

as well as their thia and aza analogs. The best results were shown by derivatives **37**–**43** (Fig. 19) which were superior in activity to ribavirin (Table 9). It was noted that derivatives of *S*-acetamides are inferior in activity to the corresponding *N*-acetamide derivatives.[26]

2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ones **44** (Fig. 20) demonstrated high activity against human cytomegalovirus and polyoma virus.[27]

The presented data clearly illustrate the trends in the design of quinazoline antiviral agents and summarize information on the nature of groups that are advisable to be introduced into 2,3- and 2,4-disubstituted quinazolines as well as quinazoline-2,4-diones to obtain active derivatives.



44
R^1 = NO_2, CN; R^2 = H, Me

Figure 20. The structures of 2-(thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ones **44**.

To conclude, quinoline and quinoxaline derivatives are active against a large number of RNA viruses. Quinolines and quinoxalines are of interest for the development of drugs that block one of the stages of HIV life cycle. Among them, new inhibitors of reverse transcriptase, RNase H and HIV integrase, as well as inhibitors of HIV penetration into the target cell have been identified. Quinolines and quinoxalines have also been found to be active against RNA viruses such as arboviruses and enteroviruses. Quinoline derivatives are promising for the development of new anti-influenza drugs against oseltamivir-resistant virus strains.

Quinazolin-4-one derivatives are characterized by activity against DNA viruses: adenovirus, hepatitis B virus, varicella zoster virus, and cytomegalovirus. Apparently, the structural similarity with purines determines the ability to inhibit DNA polymerase in the same way as acyclovir. Recently, successful examples of the design of anti-influenza agents based on 4-substituted quinazolines are noted.

The data presented in the review indicate the enormous potential of benzazines in the design of drugs suitable for the treatment of diseases caused by RNA and DNA viruses.

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