European Journal of Medicinal Chemistry 214 (2021) 113208

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis and antiviral activity of a series of novel quinoline derivatives as *anti*-RSV or *anti*-IAV agents

Minghua Wang [a, 1], Guoning Zhang [a, 1], Jianyuan Zhao [a], Ningning Cheng [b], Yujia Wang [a], Yuanhui Fu [b], Yanpeng Zheng [b], Juxian Wang [a], Mei Zhu [a], Shan Cen [a, **], Jinsheng He [b, ***], Yucheng Wang [a, *]

[a] Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100050, China
[b] College of Life Sciences and Bioengineering, Beijing Jiaotong University, Beijing, 100044, China

ARTICLE INFO

Article history:
Received 15 January 2020
Received in revised form
24 November 2020
Accepted 12 January 2021
Available online 27 January 2021

Keywords:
Quinoline derivatives
Synthesis
Anti-RSV
Anti-IAV
Structure-activity relationships

ABSTRACT

We report herein the synthesis of a series of novel quinoline derivatives, based on the lead compound **1a**, identified from a rRSV-mGFP high-throughput screening assay. Our results revealed that target compounds **1b**, **1g-h**, **1af** and **1ah** (IC_{50} = 3.10–6.93 μM) had good *in vitro* activity against RSV, which were better than **1a** and ribavirin. In addition, we found that compound **1g** displayed the lower cytotoxicity (CC_{50}: 2490.33 μM) and the highest selective index (SI = 673.06), suggesting its promising potential as a candidate for further development. On the other hand, compounds **1a**, **1m**, **1v**, **1ad-1af** and **1ah-1ai** (IC_{50}s: 1.87–14.28 μM) were more active against IAV than or comparable to ribavirin (IC_{50}: 15.36 ± 0.93 μM). Particularly, the most active compound **1ae** (IC_{50}: 1.87 ± 0.58 μM) was found to be 8.2-fold more potent than the reference drug, which could inhibit the virus transcription and replication cycle at an early stage.

1. Introduction

Over the course of human civilization and globalization, viral infections have caused millions of human casualties worldwide, and the prevention and treatment of viral diseases are a global public health challenge [1]. Respiratory syncytial virus (RSV), a negative sense single-stranded RNA virus in the *paramyxoviridae* family [2], is a leading viral cause of hospitalization due to acute lower respiratory infection especially in infants and young children [3]. In addition, RSV can cause severe illness in the elderly people and those adults with cardiopulmonary diseases or immunocompromised [4]. Currently available options (palivizumab and ribavirin) for preventing and treating RSV are limited to select populations in high-resource settings (Fig. 1). As a humanized monoclonal antibody against RSV fusion protein, Palivizumab was approved for prophylaxis in high-risk infants in 1998. However, palivizumab showed no efficacy in the treatment of established RSV infection [5]. Ribavirin is the only approved antiviral therapy for RSV infection. It is rarely used in clinic due to limited efficacy and side effects [6]. Above all, safe and effective therapy for RSV infection is still a high unmet medical need.

As a linear, negative-sense, single-stranded RNA virus, influenza virus belongs to the *orthomyxoviridae* family, which could also cause acute respiratory infectious diseases and remains serious public health problems worldwide [7]. It can be divided into four classes, A, B, C and D. Influenza A viruses (IAV) possess high pathogenicity and are the main cause of annual epidemics and occasional pandemics of respiratory diseases worldwide [8–10]. These annual epidemics are estimated to result in approximately 3–5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths [11].

Currently, three classes of anti-influenza drugs have been approved by the FDA, namely, M2 ion-channel blockers (amantadine and rimantadine), neuraminidase inhibitors (oseltamivir, zanamivir, peramivir and laninamivir octanoate) and cap-dependent endonuclease (CEN) inhibitor (baloxavir marboxil, BXM) (Fig. 1) [12,13]. In addition, Favipiravir, which inhibits the RNA dependent RNA polymerase of multiple RNA viruses, was approved

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: shancen@imb.pumc.edu.cn (S. Cen), jshhe@bjtu.edu.cn (J. He), wangyucheng@imb.pumc.edu.cn (Y. Wang).
[1] These authors made equal contributions to this work.

https://doi.org/10.1016/j.ejmech.2021.113208
0223-5234/

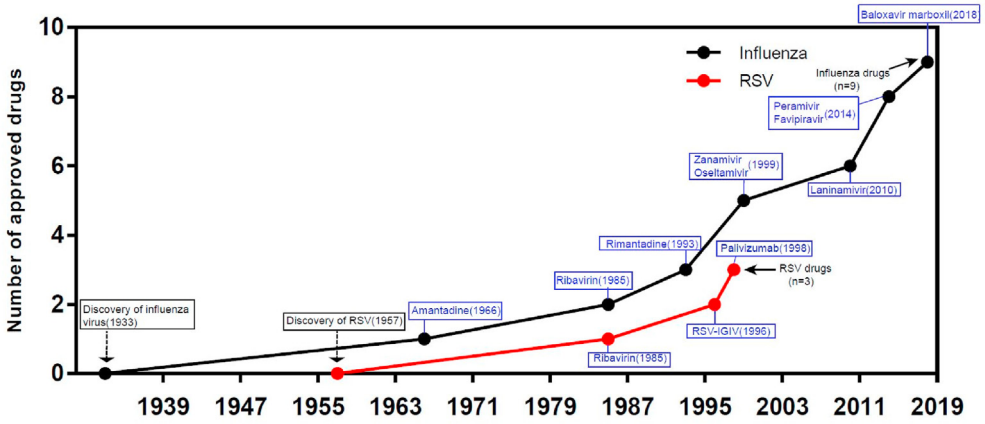


Fig. 1. Timeline of approval of drugs against RSV and influenza virus. The x axis indicates the period from January 1930 to August 2019, and the y axis shows the total number of approved drugs.

by Japan against influenza infection in 2014 (Fig. 1) [14]. However, the M2 ion-channel inhibitors are no longer recommended for treatment of influenza and NA inhibitors have several limitations in clinical practice due to their severe drug resistance and side effects [15–19]. Therefore, we are constantly required to develop new antiviral agents with new scaffold and novel mechanism of action.

In previous work, leading compound **1a** (Fig. 2) containing quinoline scaffold, was identified as potent RSV inhibitors from a rRSV-mGFP high-throughput screening assay. It exhibited considerable *anti*-RSV activity (IC_{50}: 55.75 μM) and low toxicity (CC_{50}: 539.5 μM), which encouraged us to explore its preliminary structure-activity relationship (SAR) study against RSV. As known to all, heterocyclic scaffolds play a significant role in antiviral drugs, aside from diverse pharmacological profiles, like pyrimidine-fused heterocycles [20], diaminothiophene [21] and quinoline which were reported as potential antiviral agents. Besides, quinoline derivatives have also proved active against several viruses, such as coronaviruses [22,23], respiratory syncytial virus [24], Zika virus [25] and human immunodeficiency virus [26]. Inspired by the promising antiviral activity of quinoline scaffold, we intend to synthesis new quinoline derivatives based on compound **1a** and evaluate their *in vitro anti*-RSV and IAV activities, which were expected to explore structure-activity relationships (SAR), and identify alternative candidate as antiviral agents.

2. Results and discussion

2.1. Chemistry

Quinoline derivatives **1a**–**1y** described herein were mostly prepared according to the procedure shown in Scheme 1. Starting with 2,8-dihydroxylquinoline **2**, chlorination with thionyl chloride in dimethylformamide gives 2-chloroquinoline **3**, which was followed by substitution with pyrrolidine to afford the key intermediate **4**. Nucleophilic substitution of intermediate **4** with ethyl bromoacetate in the presence of potassium carbonate yielded the

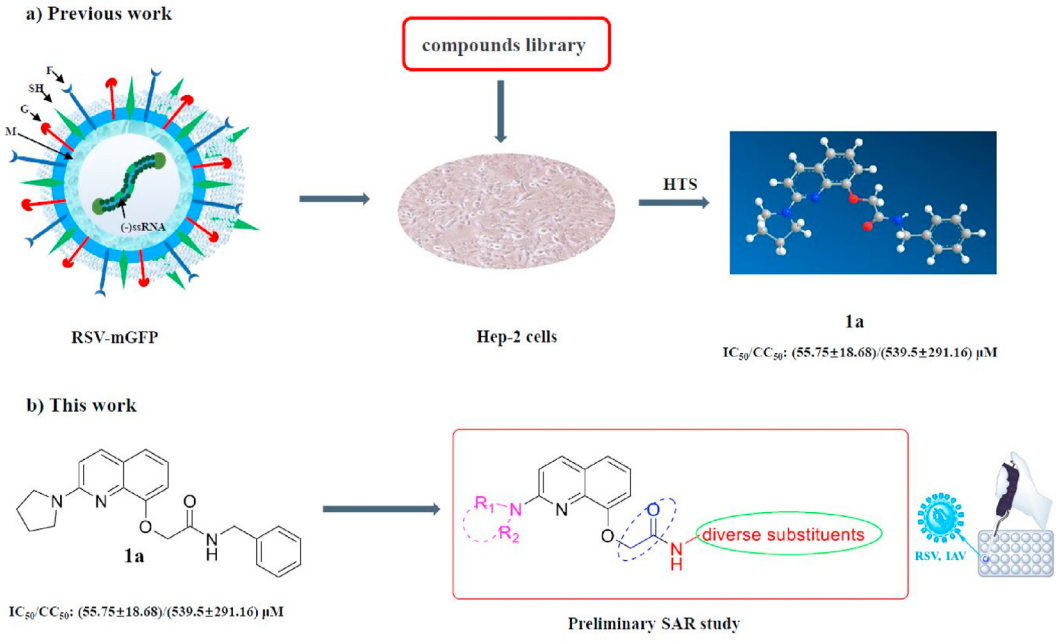
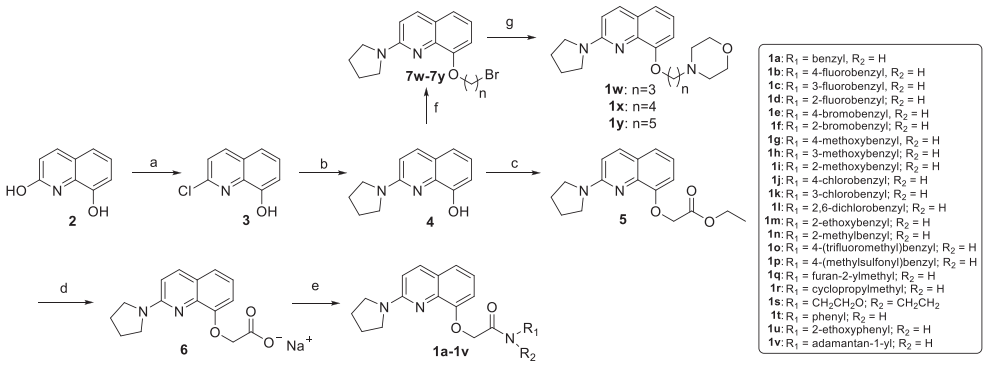


Fig. 2. Quinolines originating from rRSV-mGFP high-throughput screening platform.



Reagents and conditions: a) $SOCl_2$, DMF, 60°C; b) pyrrolidine, K_2CO_3,DMF, 110°C; c) ethyl bromoacetate, K_2CO_3, DMF, 65°C; d) NaOH, CH_3CH_2OH/H_2O; e) R_1R_2NH, HBTU, DIPEA, DMF; f) 1,3-Dibromopropane or 1,4-Dibromobutane or 1,5-dibromopentane, Cs_2CO_3, DMF, r.t.; g)morpholine, K_2CO_3, DMF, 60°C.

Scheme 1. Synthesis of the target compounds **1a-1y**.

corresponding compound **5**, which was followed by hydrolysis gave the sodium carboxylate **6**. Finally, Amidation of sodium salt **6** with different amines in the presence of O-Benzotriazole-N,N,N′,N′-tetramethyl-uronium- hexafluorophosphate (HBTU) and N,N-diisopropylethylamine (DIPEA) afforded the amides **1a**–**1v**. Compounds **1w**–**1y** with the alkyl linker were also synthesized from alkyl bromide **7w**–**7y**, which can be easily prepared through the nucleophilic substitution of **4** and dibromoalkane (Scheme 1).

The synthesis of quinoline derivatives **1aa**–**1ai** are shown in Scheme 2. Commercially available benzylamine **8** were acylated with bromoacetyl bromide **9** to afford the corresponding 2-bromo-N-(substituted phenyl) acetamides **10**, which underwent a coupling reaction with 2-chloroquinoline **3** to generate the key intermediate **11**. Condensation of **11** with available amines in the presence of potassium carbonate to provide the target compounds **1aa**–**1ai**.

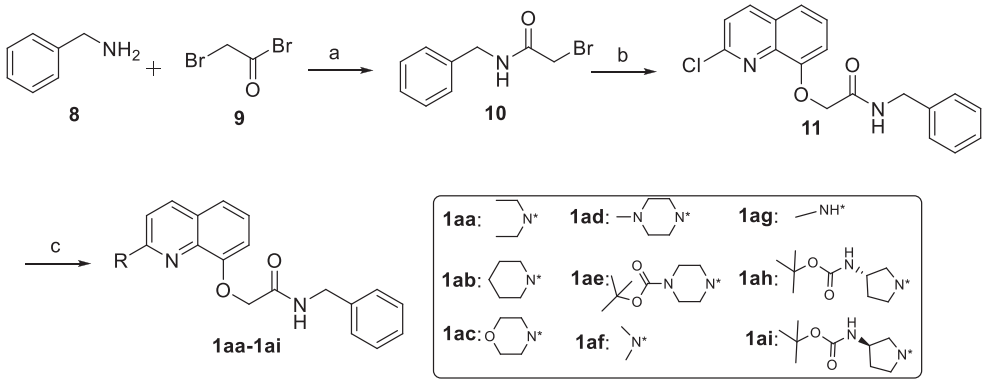
2.2. Anti-RSV activity

The target compounds **1a**–**1y** and **1aa**–**1ai** were evaluated for their *anti*-RSV activity in HEp-2 cells. The IC_{50} values of the qunoline derivatives along with ribavirin for comparison were summarized in μM in Tables 1 and 2.

Surprisingly, all the target compounds (IC_{50} < 50 μM) were more active against the RSV than the lead compound **1a**, with the exception of **1c**, **1f** and **1p**, which exhibited higher IC_{50} values of 2919 μM, 182 μM and 220 μM. Among the target compounds, **1b**, **1d**, **1g**–**h**, **1t**, **1w**–**x**, **1ae**–**ah** exhibited potent activity (IC_{50} < 17 μM). In particular, compounds **1b**, **1g**–**h**, **1af** and **1ah** (IC_{50} = 3.10–6.93 μM) were found to be 2.5–5.6-fold more potent than the reference ribavirin.

Generally, for the benzyl part, compounds bearing a substituent on the para-position of the benzyl generally showed higher activities than the corresponding ortho- or meta-substituent analogues (**1b** *vs* **1c** *vs* **1d**, **1g** *vs* **1h**, **1j** *vs* **1k**) and the contribution of the para-position substituent group to the activity was in this order: methoxyl > F > CF_3 > Cl > methylsulfonyl. When the benzyl was converted into furan-2-ylmethyl (**1q**), cyclopropylmethy (**1r**) or phenyl (**1t**), all compounds displayed potent activity, which were found more potent than that of **1a**, but less than that of ribavirin. The introduction of ethyoxyl on the 2-position of benzyl and phenyl did not bring about significant changes in activity (**1a** *vs* **1m**, **1t** *vs* **1u**). Additionally, the influence of the acyl chain was investigated. When it was replaced by the corresponding ether chain (**1w**, **1x**, and **1y**), the increase of some activity was observed, indicating that its carbonyl group was not necessary for the activity.

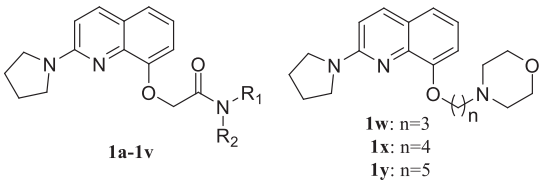
For the 2-position of quinoline ring part, the replacement of the pyrrolidinyl group by the piperidyl (**1 ab**), morpholine (**1ac**), N-methylpiperazinyl (**1ad**), and methylamino (**1 ag**) generally enhanced the antivirus activities of the compounds. Whereas the dimethylamino (**1af)** and the (*S*)-boc-3-amnio-pyrrolidinyl (**1ah**) derivatives showed significantly increased IC_{50} values (3.10 μM, 4.57 μM, respectively). The (*3R*)-configured **1ai** showed a significantly decreased *anti*-RSV activity (7.7-fold) compared to (*3S*)-configured **1ah**.



Reagents and conditions: a) triethylamine, DCM, -5°C; b) **3**, K_2CO_3, DMF, 60°C; c) RH, K_2CO_3, DMF, 110°C.

Scheme 2. Synthesis of the target compounds **1aa-1ai**.

Table 1
Anti-RSV activity and cytotoxicity of the target compounds**1a**–**1y**.



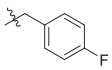
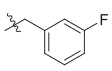
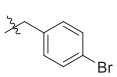
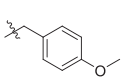
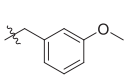
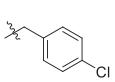
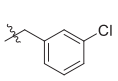
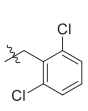
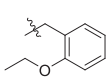
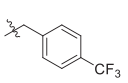
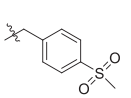
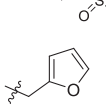
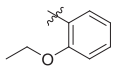
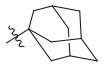
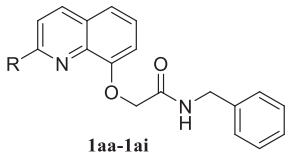
Compds.	R_1	R_2	IC_{50} (μM)	CC_{50} (μM)	SI
1a		H	55.75 ± 18.68	539.5 ± 291.16	9.68
1b		H	4.41 ± 3.05	2131.67 ± 433.00	483.37
1c		H	2919.33 ± 1622.62	443.6 ± 2787.81	0.15
1d		H	16.48 ± 5.26	20.57 ± 6.38	1.25
1e		H	ND	ND	NA
1f		H	182.25 ± 131.28	311.87 ± 85.41	1.71
1g		H	3.70 ± 1.78	2490.33 ± 984.34	673.06
1h		H	6.93 ± 4.40	74.31 ± 61.13	10.72
1i		H	ND	ND	NA
1j		H	39.18 ± 19.43	245.11 ± 161.93	6.26
1k		H	30.24 ± 16.70	72.96 ± 60.00	2.41
1l		H	ND	ND	NA
1m		H	45.69 ± 19.40	113.18 ± 62.71	2.48
1n		H	ND	ND	NA
1o		H	27.76 ± 21.39	326.8 ± 151.21	11.77
1p		H	220.90 ± 6.28	1356 ± 130.17	6.14
1q		H	22.89 ± 5.19	249.33 ± 93.29	10.89

Table 1 (*continued*)

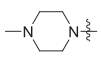
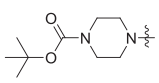
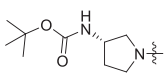
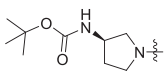
Compds.	R_1	R_2	IC_{50} (μM)	CC_{50} (μM)	SI
1r		H	28.98 ± 11.05	579.96 ± 352.83	20.01
1s	CH_2CH_2O	CH_2CH_2	ND	ND	NA
1t		H	16.54 ± 5.75	303.54 ± 254.89	18.35
1u		H	33.16 ± 23.47	1043.6 ± 491.56	31.47
1v		H	ND	ND	NA
1w	–	–	14.07 ± 7.24	551.60 ± 698.69	39.20
1x	–	–	11.60 ± 4.35	691.17 ± 409.95	59.58
1y	–	–	31.33 ± 13.78	173.02 ± 144.56	5.52
5	–	–	16.41 ± 8.47	826.03 ± 67.48	50.34
ribavirin	–	–	17.33 ± 0.06	3039.67 ± 1336.69	175.40

ND, not detected; NA, not available.

Table 2
Anti-RSV activity and cytotoxicity of the target compounds**1aa-1ai**.



1aa-1ai

Compds.	R	IC_{50} (μM)	CC_{50} (μM)	SI
1aa		ND	ND	NA
1 ab		26.11 ± 7.05	1740.33 ± 493.19	66.65
1ac		36.05 ± 16.96	46.22 ± 24.95	1.28
1ad		19.27 ± 3.02	263.83 ± 144.64	13.69
1ae		16.92 ± 9.79	1368.33 ± 1166.85	80.87
1af		3.10 ± 1.61	167.76 ± 114.79	54.12
1 ag		10.30 ± 6.50	94.81 ± 107.73	9.20
1ah		4.57 ± 2.46	43.83 ± 23.56	9.59
1ai		35.29 ± 11.26	58.56 ± 25.72	1.66
11	Cl	20.66 ± 11.40	528.20 ± 151.77	25.57
ribavirin		17.33 ± 0.06	3039.67 ± 1336.69	175.40

ND, not detected; NA, not available.

2.3. Anti-IAV activity

We also assessed the *anti*-IAV effect of these compounds and found that the most potent compounds **1ae**, **1ah** and **1ai** showed an inhibition of more than 70% towards IAV A/WSN/33 (H1N1) at a concentration of 10 μM (Fig. 3).

According to the result of preliminary screening, the IC_{50} values of the selected qunoline derivatives along with ribavirin for comparison were summarized in μM in Table 3. The selected target compounds had potent *in vitro anti*-IAV activity. Among them, compounds **1a**, **1m**, **1v**, **1ad**−**1af** and **1ah**−**1ai** (IC_{50}s: 1.87−14.28 μM) were more active than or comparable to ribavirin (IC_{50}: 15.36 ± 0.93 μM). In particular, the most active compound **1ae** (IC_{50}: 1.87 ± 0.58 μM) was found to be 8.2-fold more potent than the reference drug. These compounds had a little correlation between *anti*-RSV activity and *anti*-IAV activity.

As shown in Fig. 3 and Table 3, **1b**−**1d**, **1h**, **1j**, **1l** and **1q**−**1r** had no activity against IAV. Surprisingly, the introduction of F, Cl markedly reduced or even lost activity and replacing the benzyl (**1a**) by furan-2-ylmethyl (**1q**) or cyclopropylmethy (**1r**) lead to the loss of *anti*-IAV activity. Although a simple SAR was difficult to explore, substitution on different position of the benzene ring was crucial for their anti IAV effect. When a substitution group was introduced into these molecules on the benzene ring, compounds displayed decreased or equivalent antiviral effects. Compounds with a 2-ethoxyl substitution on the benzene ring (**1m**) and adamantly (**1v**) showed relatively higher activity than the corresponding **1a**.

Furthermore, we kept benzyl and investigated the effect of the substitution groups at C-2 position on quinoline ring. N-benzyl-2-(quinolin-8-yloxy)acetamides **1aa**−**1ai** generally exhibited *in vitro* activity, which indicated that converting pyrrolidinyl to other amine groups was permitted at the C-2 position. The activity imparted to the quinoline ring by amino group was as follows: boc-piperazinyl > boc-3-amnio-pyrrolidinyl > methyl piperazinyl > dimethylamino > diethylin > morpholine > methylamino > piperidinyl, which suggested that simply increasing the hydrophilicity could improve the activity. The configuration of C′-3 on pyrrolidine ring had almost similar effect against IAV (**1ah** *vs* **1ai**), which was contrary to that against RSV. Among them, compound **1ae** (IC_{50} = 1.87 ± 0.58 μM) demonstrated to be more potent than the lead compound **1a**.

2.4. Molecular docking studies of compound *1g* against RSV

To further understand the molecular basis of the inhibitory properties of quinoline derivatives against RSV, we docked the

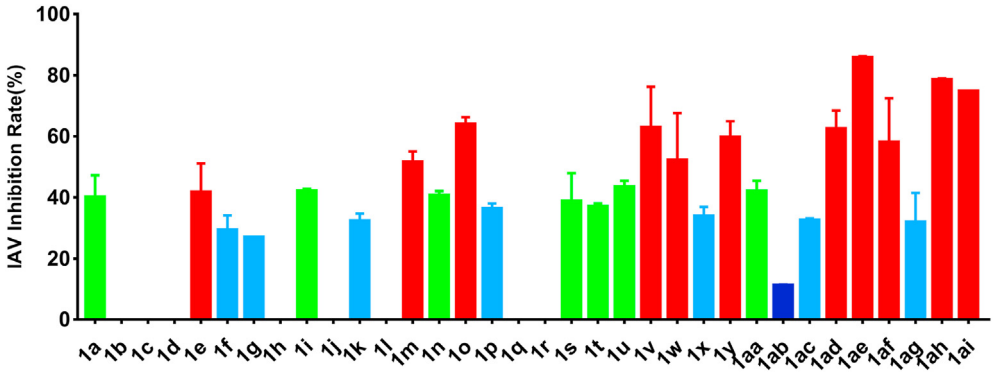


Fig. 3. Inhibition rate of the target compounds on IAV. The IAV inhibition rates were calculated by GraphPad Prism 7.

Table 3
Anti-IAV activity and cytotoxicity of the selected compounds.

Compds.	IC_{50} (μM)	CC_{50} (μM)	SI
1a	13.34 ± 0.43	>100	>7.50
1e	42.31 ± 3.75	>100	>2.36
1m	7.46 ± 0.09	>100	>13.40
1o	36.05 ± 2.30	>100	>2.77
1v	11.46 ± 1.13	>100	>8.73
1w	50.66 ± 6.33	>100	>1.97
1y	32.42 ± 2.86	>100	>3.08
1ad	9.87 ± 0.25	>100	>10.13
1ae	1.87 ± 0.58	>100	>53.47
1af	14.25 ± 2.81	>100	>7.02
1ah	5.11 ± 0.39	57.97 ± 3.00	11.34
1ai	4.99 ± 0.44	49.87 ± 1.02	9.99
ribavirin	15.36 ± 0.93	>100	>6.51

most active compound **1g** into the same 3-fold-symmetric cavity in profusion RSV F-protein reported by Yun et al. [22], using CDOCKER of discovery studio program. As shown in Fig. 4A, compound **1g** fitted perfectly into the RSV F-protein binding site. As shown in Fig. 4B, we observed that quinoline ring and pyrrolidinyl could bind with Phe488 and Phe140 by Pi-Pi stacked and Pi-alkyl interactions, which picked more hydrophobic interaction with protein. 8-substituted group could produce hydrogen-bonding interactions with the residues Asp486, as well as Pi-Pi stacked interactions with Phe488, which might account for the essential of phenyl for *anti*-RSV activity and 15-fold potency increase compared to original lead.

2.5. Primary mechanism of compound *1ae* against IAV

The most promising compound **1ae** was selected as a representative one for the primary mechanisms of action study against the influenza virus. Firstly, to investigate the possible time-dependent inhibitory effects on influenza replication, a time-of-addition experiment for **1ae** was carried out and the results were shown in Fig. 5. When compound **1ae** was added before viral infection (from −1 to 0 h), no reduction in viral yield was observed. However, **1ae** displayed a significant inhibitory effect on influenza virus when added after viral infection, particularly in the early stage (from 2 to 6 h), suggesting that **1ae** affects the early steps of the replication cycle.

In order to further confirm the mode of action of these compounds against influenza virus, we investigated the effect on IAV RNA transcription and replication using an IAV mini-genome replicon system. As shown in Fig. 6, compound **1ae** significantly inhibited the activity of luciferase in a dose-dependent manner with IC_{50} values of 1.93 μM. The IC_{50} value of the compound on the influenza virus replication subsystem was basically equivalent to the IC_{50} value (1.87 ± 0.58 μM) of the *anti*-IAV activity, indicating that these compounds may target viral RNA transcription and replication.

3. Conclusions

In summary, the compound **1a**, identified from a rRSV-mGFP high-throughput screening assay, was selected as our lead compound which displays considerable *anti*-RSV activity (IC_{50}:

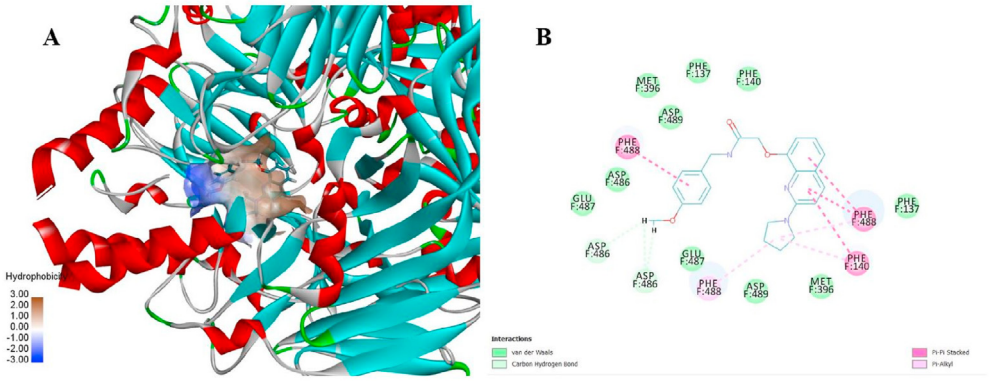


Fig. 4. Docking model of compound **1g** binding to a 3-fold symmetric cavity in prefusion RSV F glycoprotein. (A) Solid surface map of the interaction pocket with compound **1g**. Brown, blue, and white colored regions correspond to hydrophobicity. (B) 2D ligand-interaction diagram was generated in Discovery Studio 2018 software. Key bonds are indicated by dashed lines between the atoms involved, and the colors of key bonds and residues are shown according to the interaction modes.

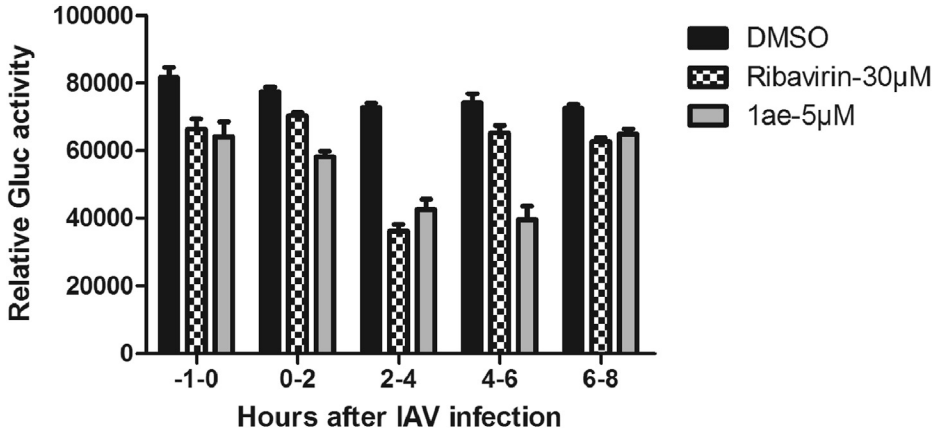


Fig. 5. Time-of-addition of **1ae** after infected with IAV. A549 cells were inoculated with influenza single-cycle A/WSN/33(H1N1) virus at a multiplicity of infection of 0.2 and compound **1ae** (5 μM) was added. Viral yields were determined at 11 h post infection by measuring Gluc activity. In this experiment, DMSO was used as the negative control and ribavirin (30 μM) as the positive control.

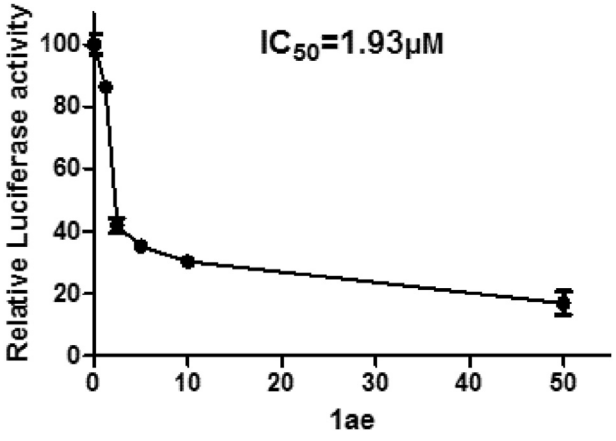


Fig. 6. Inhibition of compound **1ae** on influenza viral vRNP. HEK239T cells were transfected with pCAGGS expression plasmids encoding PB2、PB1、PA、NP、pol-LUC and SV40-Relina in the absence or presence of compound 1ae at the indicated concentration. Effect of vRNA transcription was evaluated by measuring luciferase and relina at 24h post-transfection.

55.75 μM). A series of novel quinoline derivatives with diverse substituents at C-2 and C-8 position were synthesized and evaluated for their antiviral activity against RSV and IAV. The results revealed that compounds **1b**, **1g**–**h**, **1af** and **1ah** (IC_{50} = 3.10–6.93 μM) had good *in vitro* activity against RSV, which were better than **1a** and ribavirin. In addition, we found that compound **1g** displayed the lower cytotoxicity (CC_{50}: 2490.33 μM) and the highest selective index (SI = 673.06), suggesting its promising potential as a candidate for further development. Studies to determine the *in vivo* efficacy of **1g** are currently underway. On the other hand, compounds **1a**, **1m**, **1v**, **1ad**–**1af** and **1ah**–**1ai** (IC_{50}s: 1.87–14.28 μM) were more active against IAV than or comparable to ribavirin (IC_{50}: 15.36 ± 0.93 μM). In particular, the most active compound **1ae** (IC_{50}: 1.87 ± 0.58 μM) was found to be 8.2-fold more potent than the reference drug. In the primary mechanism against IAV, compound **1ae** could inhibit the virus transcription and replication cycle at an early stage. This study provided a foundation and an opportunity for the development of a new antiviral agent.

4. Experimental section

4.1. Chemistry

Melting points were obtained from an X4 micromelting point meter and the temperature was uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined on an on a Bruker AVANCE III 400 MHz, 500 MHz or 600 MHz spectrometer (Bruker Inc) in DMSO-d_6, CD_3OD or $CDCl_3$ using tetramethylsilane as an internal standard. High resolution mass spectra were obtained on an Autospee Ultima-TOF spectrometer. TLC was performed on silica gel plates (Merck, ART5554 60 F_{254}). Commercially available starting materials, reagents, and solvents were used without further purification.

4.1.1. The synthesis of 2-pyrrolidin-1-ylquinolin-8-ol **4**

To a suspension of 2,8-dihydroxyquinoline (**2**) (10.0 g, 62 mmol) in 50 mL of anhydrous N,N-dimethylformamide (DMF) was added thionyl chloride (17.8 mL, 248 mol) at −5 °C and the reaction mixture was heated at 50 °C for 12 h. After cooling to room temperature, the mixture was poured into ice water and extracted with ethyl acetate (50 mL × 3). The combined extracts were washed with water, saturated brine, dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give crude product 2-chloro-8-hydroxyquinoline (**3**) (7.5 g, 68% from **2**) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.0 Hz, 1H), 7.69 (brs, 1H), 7.46 (t, J = 7.0 Hz, 1H), 7.38 (t, J = 7.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.0 Hz, 1H).

To a solution of **3** (6.0 g, 33.4 mmol) and potassium carbonate (9.2 g, 66.8 mmol) dissolved in DMF (30 mL) was added pyrrolidine (4.7 g, 66.8 mmol) and stirred for 3 h at 110 °C. After cooling to room temperature, the mixture was poured into ice water (150 mL) and extracted with ethyl acetate (80 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (10:1, v/v) to get the title compound **4** (6.6 g, 92% from **3**) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 3.56 (t, J = 6.0 Hz, 4H), 2.03–1.88 (m, 4H). LC-MS (ESI), m/z:215[M+H]$^+$, 237[M+Na]$^+$.

*4.1.2. General procedure for the synthesis of compounds **1a**–**1v***

To a solution of **4** (3.0 g, 14.2 mmol) and potassium carbonate (3.9 g, 24.4 mmol) dissolved in DMF (20 mL) was added ethyl bromoacetate (3.6 g, 21.2 mmol) dropwise and stirred for 5 h at 65 °C and then poured into water (100 mL), extracted with ethyl acetate (80 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (10:1, v/v) to get compound **5** (4.2 g, 98% from **4**) as yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.10–6.93 (m, 2H), 6.85 (d, J = 9.0 Hz, 1H), 5.03 (s, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.52 (d, J = 6.0 Hz, 4H), 1.97 (q, J = 6.0 Hz, 4H), 1.20 (t, J = 7.0 Hz, 3H). LC-MS (ESI), *m/z*:301[M+H]$^+$, 323[M+Na]$^+$.

To a solution of **5** (4.3g, 14.4 mmol) in alcohol (30 mL) was added sodium hydroxide (1.2 g, 28.7 mmol) in 30 mL water at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The resulting solid was collected by filtration and washed successively with methanol (10 mL), and dried in vacuo to give the title compound **6** (3.2 g, 77%) as white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 4.68 (s, 2H), 3.63 (t, J = 6.0 Hz, 4H), 2.09 (m, 4H). LC-MS (ESI), *m/z*:273[M+H]$^+$.

A solution of compound **6** (96.2 mg, 0.32 mmol), O-Benzotriazole-N,N,N′,N′-tetramethyl-uronium-hexafluorophosphate (HBTU) (136.5 mg, 0.36 mmol) in DMF (2 mL) was stirred at room temperature under the atmosphere of nitrogen for 5 min. The substituted amines (0.36 mmol) and N,N-diisopropylethylamine (DIPEA) (0.36 mmol) was added to the mixture and stirred for 3 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed by saturated brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with hexanes/EtOAc (1:1, v/v) to give the target compounds **1a**–**1v** as white or off-white solids.

*4.1.2.1. N-benzyl-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1a**.* According to the general procedure, employing **6** and benzylamine afforded compound **1a** as a white solid, 37% yield, mp: 151–152 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.27–7.19 (m, 4H), 7.15–7.05 (m, 3H), 6.83 (d, J = 9.0 Hz, 1H), 4.79 (s, 2H), 4.38 (d, J = 6.0 Hz, 2H), 3.36 (s, 4H), 1.85 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.27, 155.12, 152.22, 140.62, 139.22, 137.54, 128.70, 127.54, 127.31, 123.89, 122.37, 121.25, 116.00, 111.52, 70.97, 46.80, 42.31, 25.37. LC-MS (ESI), *m/z*:362[M+H]$^+$, 384[M+Na]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{24}N_3O_2$ (M + H)$^+$: 362.1863; Found: 362.1851.

*4.1.2.2. N-(4-fluorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1b**.* According to the general procedure, employing **6** and 4-fluorobenzylamine afforded compound **1b** as a white solid, 38% yield, mp: 140–142 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.18–7.13 (m, 2H), 7.12–7.02 (m, 3H), 6.83 (d, J = 9.0 Hz, 1H), 4.78 (s, 2H), 4.35 (t, J = 6.0 Hz, 2H), 3.37 (s, 4H), 1.87 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.28, 155.09, 152.18, 140.61, 137.57, 135.46, 129.61, 123.90, 122.41, 121.25, 116.08, 115.49, 115.35, 111.49, 70.97, 46.80, 41.62, 25.37. LC-MS (ESI), *m/z*: 380[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}FN_3O_2$ (M + H)$^+$: 380.1769; Found: 380.1773.

*4.1.2.3. N-(3-fluorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1c**.* According to the general procedure, employing **6** and 3-fluorobenzylamine afforded compound **1c** as a white solid, 57% yield, mp: 132–133 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29–7.25 (m, 2H), 7.09 (t, J = 8.0 Hz, 1H), 7.06–7.01 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 10.0 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 4.81 (s, 2H), 4.39 (t, J = 6.0 Hz, 2H), 3.43–3.34 (m, 4H), 1.91–1.80 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.46, 162.59, 155.10, 152.21, 142.32, 140.63, 137.59, 130.62, 123.94, 123.54, 122.49, 121.27, 116.29, 114.12, 111.50, 71.09, 46.82, 41.80, 25.36. LC-MS (ESI), *m/z*: 380[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}FN_3O_2$ (M + H)$^+$: 380.1769; Found: 380.1762.

*4.1.2.4. N-(2-fluorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1d**.* According to the general procedure, employing **6** and 2-fluorobenzylamine afforded compound **1d** as a white solid, 37% yield, mp: 136–137 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (t, J = 6.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.33–7.27 (m, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.12–7.05 (m, 4H), 6.84 (d, J = 9.0 Hz, 1H), 4.80 (s, 2H), 4.42 (d, J = 5.5 Hz, 2H), 3.41 (t, J = 6.5 Hz, 4H), 1.93–1.86 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.37, 160.49, 155.10, 152.11, 140.59, 137.55, 129.88, 129.53, 125.77, 124.70, 123.88, 122.37, 121.23, 115.89, 115.52, 111.49, 70.79, 46.79, 36.21, 25.39. LC-MS (ESI), *m/z*: 380[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}FN_3O_2$ (M + H)$^+$: 380.1769; Found: 380.1759.

*4.1.2.5. N-(4-bromobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1e**.* According to the general procedure, employing **6** and 4-bromobenzylamine afforded compound **1e** as a white solid, 34% yield, mp: 163–165 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (t, J = 6.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.12–7.02 (m, 3H), 6.83 (d, J = 9.0 Hz, 1H), 4.79 (s, 2H), 4.34 (d, J = 6.0 Hz, 2H), 3.40–3.33 (m, 4H), 1.85–1.88 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.39, 155.07, 152.17, 140.62, 138.70, 137.56, 131.55, 129.85, 123.91, 122.47, 121.27, 120.39, 116.20, 111.50, 71.04, 46.80, 41.76, 25.37. LC-MS (ESI), *m/z*: 440, 442[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}BrN_3O_2$ (M + H)$^+$: 440.0968; Found: 440.0975, 442.0954.

*4.1.2.6. N-(2-bromobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1f**.* According to the general procedure, employing **6** and 2-bromobenzylamine afforded compound **1f** as a white solid, 45% yield, mp: 148–150 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29–7.21 (m, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.16–7.06 (m, 2H), 6.82 (d, J = 9.0 Hz, 1H), 4.83 (s, 2H), 4.40 (d, J = 6.0 Hz, 2H), 3.38 (t, J = 6.5 Hz, 4H), 1.90–1.83 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.52, 155.09, 152.17, 140.66, 137.57, 137.55, 132.85, 129.50, 129.33, 128.07, 123.95, 122.84, 122.45, 121.27, 116.08, 111.51, 70.92, 46.82, 42.81,25.38. LC-MS (ESI), *m/z*: 440, 442[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}BrN_3O_2$ (M + H)$^+$: 440.0968; Found: 440.0980, 442.0945.

*4.1.2.7. N-(4-methoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1g**.* According to the general procedure, employing **6** and 4-methoxybenzylamine afforded compound **1g** as a white solid, 39% yield, mp: 139–141 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.13–7.00 (m, 3H), 6.88–6.73 (m, 3H), 4.76 (s, 2H), 4.29 (d, J = 6.0 Hz, 2H), 3.72 (s, 4H), 3.35 (s, 3H), 1.86 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.06, 158.72, 155.10, 152.16, 140.58, 137.51, 131.01, 128.99, 123.85, 122.30, 121.22, 115.77, 114.11, 111.51, 70.83, 55.53, 46.78, 41.86, 25.37. LC-MS (ESI), *m/z*: 392 [M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{26}N_3O_3$ (M + H)$^+$: 392.1969; Found: 392.1954.

*4.1.2.8. N-(3-methoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1h**.* According to the general procedure, employing

6 and 3-methoxybenzylamine afforded compound **1h** as a white solid, 56% yield, mp: 98–100 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 9.0 Hz, 1H), 6.77 (dd, J = 8.0, 3.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 4.80 (s, 2H), 4.35 (d, J = 6.0 Hz, 2H), 3.62 (s, 3H), 3.37 (t, J = 6.5 Hz, 4H), 1.87–1.85 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.28, 159.71, 155.10, 152.26, 140.78, 140.63, 137.52, 129.73, 123.90, 122.40, 121.24, 119.74, 116.09, 113.06, 112.84, 111.51, 71.06, 55.31, 46.80, 42.31, 25.36. LC-MS (ESI), *m/z*: 392 [M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{26}N_3O_3$ (M + H)$^+$: 392.1969; Found: 392.1955.

4.1.2.9. N-(2-methoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1i****.* According to the general procedure, employing **6** and 2-methoxybenzylamine afforded compound **1i** as a white solid, 60% yield, mp: 103–105 °C.^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.26–7.18 (m, 2H), 7.09 (t, J = 8.0 Hz, 1H), 7.03–6.98 (m, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.83–6.77 (m, 2H), 4.78 (s, 2H), 4.33 (d, J = 6.0 Hz, 2H), 3.64 (s, 3H), 3.37 (t, J = 6.5 Hz,4H), 1.86 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.21, 157.14, 155.10, 152.20, 140.62, 137.49, 128.72, 128.32, 126.35, 123.86, 122.27, 121.22, 120.45, 115.71, 111.50, 110.91, 70.81, 55.62, 46.75, 37.74, 25.38. LC-MS (ESI), *m/z*: 392 [M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{26}N_3O_3$ (M + H)$^+$: 392.1969; Found: 392.1956.

4.1.2.10. N-(4-chlorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1j****.* According to the general procedure, employing **6** and 4-chlorobenzylamine benzylamine afforded compound **1j** as a white solid, 46% yield, mp: 151–153 °C.^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29–7.24 (m, 3H), 7.15–7.06 (m, 3H), 6.83 (d, J = 9.0 Hz, 1H), 4.79 (s, 2H), 4.35 (d, J = 6.0 Hz, 2H), 3.36 (t, J = 6.5 Hz, 4H), 1.90–1.84 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.39, 155.08, 152.17, 140.62, 138.30, 137.57, 131.91, 129.49, 128.64, 123.91, 122.46, 121.27, 116.19, 111.50, 71.03, 46.80, 41.69, 25.36. LC-MS (ESI), *m/z*: 396 [M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}ClN_3O_2$ (M + H)$^+$: 396.1474; Found: 396.1469, 398.1441.

4.1.2.11. N-(3-chlorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1k****.* According to the general procedure, employing **6** and 3-chlorobenzylamine afforded compound **1k** as a white solid, 51% yield, mp: 107–109 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.28–7.23 (m, 3H), 7.15–7.05 (m, 3H), 6.83 (d, J = 9.0 Hz, 1H), 4.81 (s, 2H), 4.38 (d, J = 6.0 Hz, 2H), 3.39 (t, J = 6.5 Hz, 4H), 1.89–1.85 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.50, 155.09, 152.21, 141.91, 140.62, 137.62, 133.42, 130.54, 127.35, 127.27, 126.24, 123.95, 122.55, 121.27, 116.38, 111.51, 71.16, 46.83, 41.73, 25.38. LC-MS (ESI), *m/z*: 396[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{23}ClN_3O_2$ (M + H)$^+$: 396.1474; Found: 396.1482, 398.1443.

4.1.2.12. N-(2,6-dichlorobenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1l****.* According to the general procedure, employing **6** and 2,6-dichlorobenzylamine afforded compound **1l** as a white solid, 47% yield, mp: 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.09–7.07 (m, 2H), 6.58 (d, J = 9.0 Hz, 1H), 4.82 (s, 2H), 4.77 (d, J = 5.0 Hz, 2H), 3.40 (t, J = 5.0 Hz, 4H), 1.98 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.00, 154.92, 151.75, 140.64, 137.35, 135.78, 132.73, 130.77, 129.02, 123.82, 122.15, 121.12, 115.03, 111.36, 70.09, 46.64, 39.04, 25.34. LC-MS (ESI), *m/z*:430[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{22}Cl_2N_3O_2$ (M + H)$^+$: 430.1084; Found: 430.1104, 432.1084.

4.1.2.13. N-(2-ethoxybenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1m****.* According to the general procedure, employing **6** and 2-ethoxybenzylamine afforded compound **1m** as a white solid, 31% yield, mp: 83–84 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.0 Hz, 2H), 7.09 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.82–6.76 (m, 2H), 4.78 (s, 2H), 4.32 (d, J = 6.0 Hz, 2H), 3.82 (q, J = 7.0 Hz, 2H), 3.35 (t, J = 6.5 Hz, 4H), 1.88–1.81 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.14, 156.51, 155.04, 152.23, 140.67, 137.44, 128.70, 128.43, 126.36, 123.86, 122.31, 121.19, 120.30, 115.83, 111.76, 111.48, 70.93, 63.52, 46.72, 38.03, 25.35, 14.98. LC-MS (ESI), *m/z*:406 [M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{24}H_{28}N_3O_3$ (M + H)$^+$: 406.2125; Found: 406.2115.

4.1.2.14. N-(2-methylbenzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1n****.* According to the general procedure, employing **6** and 2-methylbenzylamine afforded compound **1n** as a white solid, 35% yield, mp: 125–126 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.17–7.01 (m, 5H), 6.78 (d, J = 9.0 Hz, 1H), 4.80 (s, 2H), 4.32 (s, 2H), 3.32 (s, 4H), 1.99 (s, 3H), 1.85 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.99, 155.04, 152.09, 140.62, 137.43, 136.50, 136.16, 130.36, 128.15, 127.48, 126.05, 122.28, 121.19, 115.64, 111.49, 70.71, 46.73, 40.74, 25.34, 18.75. LC-MS (ESI), *m/z*:406[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{26}N_3O_2$ (M + H)$^+$: 376.2020; Found: 406.2016.

4.1.2.15. N-(4-(trifluoromethyl)benzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acet-amide ***1o****.* According to the general procedure, employing **6** and 4-trifluoromethylbenzylamine afforded compound **1o** as a white solid, 37% yield, mp: 176–178 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 4.82 (s, 2H), 4.47 (d, J = 6.0 Hz, 2H), 3.36 (t, J = 6.5 Hz, 4H), 1.87–1.82 (m, 4H).^{13}C NMR (151 MHz, DMSO-d_6) δ 169.58, 155.06, 152.20, 144.23, 140.64, 137.60, 128.22, 125.67, 125.53, 123.95, 122.55, 121.30, 116.43, 111.47, 71.16, 46.79, 41.90, 25.32. LC-MS (ESI), *m/z*:430[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{23}F_3N_3O_2$ (M + H)$^+$: 430.1737; Found: 430.1721.

4.1.2.16. N-(4-(methylsulfonyl)benzyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acet-amide ***1p****.* According to the general procedure, employing **6** and 4-methylsulphonylbenzyl- amine hydrochloride afforded compound **1p** as a white solid, 31% yield, mp: 189–191 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.87–7.82 (m, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.21–7.12 (m, 4H), 6.85–6.47 (m, 1H), 4.88 (s, 2H), 4.57 (d, J = 6.0 Hz, 2H), 3.39 (s, 4H), 3.00 (s, 3H), 1.90 (s, 4H). LC-MS (ESI), *m/z*:440[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{26}N_3O_4S$ (M + H)$^+$: 440.1639; Found: 440.1646.

4.1.2.17. N-(furan-2-ylmethyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide ***1q****.* According to the general procedure, employing **6** and furfurylamine afforded compound **1q** as a white solid, 52% yield, mp: 148–150 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (t, J = 6.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.49 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 6.35 (s, 1H), 6.14 (s, 1H), 4.75 (s, 2H), 4.37 (d, J = 5.5 Hz, 2H), 3.48–3.45 (m, 4H), 1.96–1.93 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.10, 155.16, 152.10, 142.76, 140.59, 137.53, 123.82, 122.32, 121.21, 115.80, 111.53, 110.81, 107.49, 70.74, 46.87, 35.65, 25.46. LC-MS (ESI), *m/z*:352[M+H]$^+$. HRMS-ESI (*m/z*): Calcd. for $C_{20}H_{22}N_3O_3$ (M + H)$^+$: 352.1656; Found: 352.1646.

*4.1.2.18. N-(cyclopropylmethyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide **1r**.* According to the general procedure, employing **6** and cyclopropanemethylamine afforded compound **1r** as a white solid, 56% yield, mp: 147–149 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (t, J = 6.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 4.68 (s, 2H), 3.56 (s, 4H), 3.05 (t, J = 6.5 Hz, 2H), 1.98 (s, 4H), 0.90–0.80 (m, 1H), 0.34 (d, J = 7.5 Hz, 2H), 0.10 (d, J = 5.0 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.84, 155.22, 152.03, 140.54, 137.60, 123.84, 122.14, 121.24, 115.25, 111.43, 70.32, 46.96, 43.08, 25.47, 11.24, 3.51. LC-MS (ESI), m/z:326[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{19}H_{24}N_3O_2$ (M + H)$^+$: 326.1863; Found: 326.1855.

*4.1.2.19. 1-Morpholino-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy) ethan-1-one **1s**.* According to the general procedure, employing **6** and morpholine afforded compound **1s** as an off-white solid, 53% yield, mp: 70–72 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 9.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.06–7.01 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H), 4.98 (s, 2H), 3.69–3.43 (m, 12H), 1.99–1.97 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.82, 155.01, 151.83, 140.46, 137.46, 123.83, 121.60, 121.07, 113.86, 111.13, 68.85, 66.69, 47.01, 45.86, 25.50. LC-MS (ESI), m/z:342[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{19}H_{24}N_3O_3$ (M + H)$^+$: 342.1812; Found: 342.1817.

*4.1.2.20. N-phenyl-2-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)acetamide **1t**.* According to the general procedure, employing **6** and aniline afforded compound **1t** as an off-white solid, 77% yield, mp: 130–132 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 2H), 7.27 (d, J = 7.5 Hz, 1H), 7.13–7.06 (m, 2H), 6.94 (d, J = 8.5 Hz, 1H), 4.92 (s, 2H), 3.59–3.49 (m, 4H), 1.93 − (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.10, 155.24, 152.05, 140.64, 138.53, 137.76, 129.24, 124.36, 124.01, 122.51, 121.31, 120.25, 116.15, 111.55, 70.82, 47.06, 25.44. LC-MS (ESI), m/z:348[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{21}H_{22}N_3O_2$ (M + H)$^+$: 348.1707; Found: 348.1698.

*4.1.2.21. N-(2-ethoxyphenyl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide **1u**.* According to the general procedure, employing **6** and 2-ethoxybenzamine afforded compound **1u** as a faint yellow solid, 33% yield, mp: 110–112 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.06 (d, J = 8.0 Hz, H), 8.01 (d, J = 7.5 Hz, H), 7.40 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 6.96–6.89 (m, 2H), 4.91 (s, 2H), 3.99 (q, J = 7.0 Hz, 2H), 3.48 (s, 4H), 1.88 (s, 4H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.67, 155.15, 151.60, 148.60, 137.55, 127.09, 125.05, 124.01, 122.67, 121.07, 120.90, 115.59, 112.57, 111.46, 70.49, 64.40, 46.84, 25.40, 14.64. LC-MS (ESI), m/z:392[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{23}H_{26}N_3O_3$ (M + H)$^+$: 392.1969; Found: 392.1960.

*4.1.2.22. N-(adamantan-1-yl)-2-((2-(pyrrolidin-1-yl)quinolin-8-yl) oxy)acetamide **1v**.* According to the general procedure, employing **6** and Amantadine afforded compound **1v** as a white solid, 50% yield, mp: 222–224 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 9.0 Hz, 1H), 7.27 (s, 1H), 7.17–7.05 (m, 2H),6.96 (d, J = 7.5 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 4.57 (s, 2H), 3.65 (s, 4H), 2.12–2.03 (m, 13H), 1.74–1.67 (m, 6H). LC-MS (ESI), m/z:406[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{25}H_{32}N_3O_3$ (M + H)$^+$: 406.2489; Found: 406.2486.

*4.1.3. General procedure for the synthesis of compounds **1w**–**1y***

A mixture of **4** (138.2 mg, 0.64 mmol), cesium carbonate (417.0 mg, 1.28 mmol) and DMF (4 mL) was stirred for 10 min at room temperature and 1,3-dibromopropane (156.3 mg, 0.77 mmol) (1,4-dibromobutane or 1,5-dibromopentane) was added, and then stirred overnight at the same temperature. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed by saturated brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the crude compounds **7w**–**7y** as yellow oils.

A mixture of **7w** (116.2 mg, 0.35 mmol), morpholine (45.3 mg, 0.52 mmol) and potassium carbonate (96.7 mg, 0.70 mmol) in DMF (2 mL) was stirred for 20 h at 50 °C under an atmosphere of nitrogen. The mixture was diluted with water and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed by saturated brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (1:2, v/v) to get compound **1w**–**1y** as off-white solids or yellow oil.

*4.1.3.1. 4-(3-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)propyl)morpholine **1w**.* According to the general procedure, employing **7w** and morpholine afforded compound **1w** as a white solid, 28% yield, mp: 84–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 4.24 (t, J = 6.5 Hz, 2H), 3.74 (t, J = 5.0 Hz, 4H), 3.64 (s, 4H), 2.69 (t, J = 8.0 Hz, 2H), 2.53 (s, 4H), 2.17 (t, J = 7.0 Hz, 2H), 2.04 (t, J = 6.0 Hz, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.91, 152.92, 140.67, 137.34, 123.74, 121.22, 120.74, 113.13, 110.85, 67.71, 66.58, 55.59, 53.84, 46.88, 37.95, 25.49. LC-MS (ESI), m/z:342 [M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{20}H_{28}N_3O_2$ (M + H)$^+$: 342.2176; Found: 342.2164.

*4.1.3.2. 4-(4-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)butyl)morpholine **1x**.* According to the general procedure, employing **7x** and morpholine afforded compound **1x** as a white solid, 22% yield, mp: 94–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 4.20 (t, J = 6.5 Hz, 2H), 3.75 (s, 4H), 3.64 (s, 4H), 2.54 (s, 6H), 2.06–1.96 (m, 6H), 1.89–1.81 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.91, 152.94, 140.54, 137.34, 123.70, 121.23, 120.53, 112.57, 110.84, 68.99, 53.48, 46.88, 37.94, 27.29, 25.49. LC-MS (ESI), m/z:356[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{21}H_{30}N_3O_2$ (M + H)$^+$: 356.2333; Found: 356.2334.

*4.1.3.3. 4-(5-((2-(pyrrolidin-1-yl)quinolin-8-yl)oxy)pentyl)morpholine **1y**.* According to the general procedure, employing **7y** and morpholine afforded compound **1y** as a yellow oil, 31% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 9.0 Hz, 1H), 4.17 (t, J = 6.5 Hz, 2H), 3.72 (t, J = 5.0 Hz, 4H), 3.63 (s, 4H), 2.46 (s, 4H), 2.39 (t, J = 7.0 Hz, 2H), 2.04 (s, 4H), 1.99 (t, J = 7.0 Hz, 2H), 1.62 (s, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.90, 153.03, 140.62, 137.33, 123.72, 121.22, 120.55, 112.74, 110.81, 69.30, 66.47, 58.68, 53.71, 46.86, 37.94, 29.38, 25.50, 24.11. LC-MS (ESI), m/z:370 [M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{22}H_{32}N_3O_2$ (M + H)$^+$: 370.2489; Found: 370.2484.

*4.1.4. General procedure for the synthesis of compounds **1aa**–**1ai***

To a solution of benzylamine (**8**) (1.3g, 12.1 mmol) and triethylamine (1.5 g, 14.5 mmol) dissolved in dichloromethane (8 mL) was added bromoacetyl bromide (2.7 g, 13.3 mmol) dropwise at −10 °C and then stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (8:1, v/v) to get compound **10** (0.97 g, 35%) as off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (t, J = 6.0 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.29–7.22 (m, 3H), 4.30 (d, J = 5.9 Hz, 2H), 3.91 (s, 2H). LC-MS (ESI), m/z:228[M+H]$^+$.

To a solution of **3** (0.69 g, 3.86 mmol) and potassium carbonate (1.07 g, 7.72 mmol) dissolved in DMF (5 mL) was added **10** (0.97 g,

4.24 mmol) and stirred for 2 h at 65 °C and then poured into water (50 mL), extracted with ethyl acetate (40 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (1:1, v/v) to get compound **11** (1.24 g, 98% from **3**) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (t, J = 6.0 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 7.62 (t, J = 9.0 Hz, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.27–7.21 (m, 4H), 4.84 (s, 2H), 4.36 (d, J = 6.0 Hz, 2H). LC-MS (ESI), *m/z*:327 $[M+H]^+$.

To a solution of **11** (134.2 mg, 0.41 mmol) and potassium carbonate (113.3 mg, 0.82 mmol) dissolved in DMF (3 mL) was added secondary amines (0.82 mmol) and stirred for 8 h at 110 °C. After cooling to room temperature, the mixture was poured into water (30 mL) and extracted with ethyl acetate (15 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluting with petroleum ether and ethyl acetate (1:1, v/v) to get the target compound **1aa**–**1ai**.

4.1.4.1. N-benzyl-2-((2-(diethylamino)quinolin-8-yl)oxy)acetamide ***1aa***. According to the general procedure, employing **11** and diethylamine afforded compound **1aa** as an off-white solid. Due to the low boiling point of diethylamine, the reaction was incomplete resulting in a lower yield of 12%. mp: 107–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.25–7.17 (m, 6H), 7.12–7.01 (m, 2H), 6.80 (d, J = 9.0 Hz, 1H), 4.80 (s, 2H), 4.55 (d, J = 6.0 Hz, 2H), 3.48 (q, J = 7.0 Hz, 4H), 1.10 (t, J = 7.0 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.87, 156.01, 144.04, 138.56, 138.06, 134.38, 130.03, 128.63, 128.60, 128.52, 127.38, 123.68, 120.81, 110.53, 60.44, 52.26, 42.73, 13.53. LC-MS (ESI), *m/z*:364$[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{26}N_3O_2$ $(M+H)^+$: 364.2020; Found: 364.2016.

4.1.4.2. N-benzyl-2-((2-(piperidin-1-yl)quinolin-8-yl)oxy)acetamide ***1 ab***. According to the general procedure, employing **11** and piperidine afforded compound **1 ab** as a white solid, 31% yield, mp: 167–169 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.74 (d, J = 5.0 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 6.5 Hz, 1H), 7.29–7.08 (m, 9H), 4.77 (s, 2H), 4.38 (d, J = 5.0 Hz, 2H), 3.58 (d, J = 4.5 Hz, 4H), 1.62–1.53 (m, 2H), 1.52–1.41 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.09, 156.96, 152.20, 139.97, 139.40, 137.94, 128.72, 127.45, 127.28, 124.08, 121.98, 121.91, 115.28, 111.08, 70.53, 45.92, 42.22, 25.67, 24.72. LC-MS (ESI), *m/z*:376$[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{26}N_3O_2$ $(M+H)^+$: 376.2020; Found: 376.2027.

4.1.4.3. N-benzyl-2-((2-morpholinoquinolin-8-yl)oxy)acetamide ***1ac***. According to the general procedure, employing **11** and morpholine afforded compound **1ac** as a white solid, 31% yield, mp: 153–155 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (t, J = 6.0 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.29–7.20 (m, 5H), 7.19–7.14 (m, 3H), 4.78 (s, 2H), 4.39 (d, J = 6.5 Hz, 2H), 3.60 (t, J = 5.0 Hz, 4H), 3.52 (t, J = 5.0 Hz, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.79, 157.61, 143.33, 138.46, 138.38, 135.00, 130.12, 128.68, 128.53, 127.61, 127.37, 124.44, 122.14, 110.95, 66.43, 60.47, 52.35, 45.26. LC-MS (ESI), *m/z*:378$[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{22}H_{24}N_3O_3$ $(M+H)^+$: 378.1812; Found: 378.1821.

4.1.4.4. N-benzyl-2-((2-(4-methylpiperazin-1-yl)quinolin-8-yl)oxy) acetamide ***1ad***. According to the general procedure, employing **11** and N-methylpiperazine afforded compound **1ad** as a white solid, 47% yield, mp: 154–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 7.0 Hz, 2H), 7.20–7.13 (m, 3H), 7.11 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 4.82 (s, 2H), 4.54 (d, J = 6.0 Hz, 2H), 3.60 (s, 4H), 2.38 (s, 4H), 2.32 (s, 3H).^{13}C NMR (151 MHz, DMSO-d_6) δ 169.00, 156.89, 152.30, 139.67, 139.41, 138.12, 128.74, 127.46, 127.31, 124.38, 122.42, 121.84, 115.01, 110.98, 70.34, 54.64, 45.89, 44.62, 42.20. LC-MS (ESI), *m/z*:391 $[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{23}H_{27}N_4O_2$ $(M+H)^+$: 391.2129; Found: 391.2125.

4.1.4.5. Tert-butyl 4-(8-(2-(benzylamino)-2-oxoethoxy)quinolin-2-yl)piperazine-1- carboxylate ***1ae***. According to the general procedure, employing **11** and N-bocpiperazine afforded compound **1ae** as a white solid, 23% yield, mp: 152–154 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.63 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.39 (dd, J = 6.5, 1.0 Hz, 1H), 7.30–7.13 (m, 8H), 4.77 (s, 2H), 4.40 (d, J = 5.0 Hz, 2H), 3.60–3.54 (m, 4H), 3.39–3.33 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.90, 156.80, 154.38, 152.25, 139.56, 139.44, 138.21, 128.74, 127.49, 127.33, 124.46, 122.55, 121.80, 114.89, 111.05, 79.52, 70.21, 44.71, 42.20, 40.45, 28.57. LC-MS (ESI), *m/z*:477 $[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{27}H_{33}N_4O_4$ $(M+H)^+$: 477.2497; Found: 477.2508.

4.1.4.6. N-benzyl-2-((2-(dimethylamino)quinolin-8-yl)oxy)acetamide ***1af***. According to the general procedure, employing **11** and dimethylamine afforded compound **1af** as a white solid, 74% yield, mp: 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.89 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 5.0 Hz, 4H), 7.17 (s, 3H), 6.88 (s, 1H), 4.87 (s, 2H), 4.56 (d, J = 6.0 Hz, 2H), 3.04 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.10, 157.13, 152.17, 140.13, 139.30, 137.77, 128.71, 127.60, 127.31, 123.73, 122.09, 121.58, 115.55, 110.38, 70.65, 42.35, 37.96. LC-MS (ESI), *m/z*:336$[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{20}H_{22}N_3O_2$ $(M+H)^+$: 336.1707; Found: 336.1704.

4.1.4.7. N-benzyl-2-((2-(methylamino)quinolin-8-yl)oxy)acetamide ***1 ag***. According to the general procedure, employing **11** and methylamine afforded compound **1 ag** as an off-white solid. Because of the low boiling point of methylamine and the use of methylamine in ethanol solution, the reaction was incomplete and there was a secondary reaction with ethanol resulting in a lower yield of 10%. mp: 113–114 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.04 (d, J = 5.0 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 6.5 Hz, 1H), 7.27–7.18 (m, 4H), 7.17–7.14 (m, 2H), 7.08 (t, J = 6.5 Hz, 2H), 6.74 (d, J = 7.5 Hz, 1H), 4.78 (s, 2H), 4.38 (d, J = 5.0 Hz, 2H), 2.76 (d, J = 4.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.31, 157.47, 152.31, 140.38, 139.44, 136.85, 128.71, 127.47, 127.28, 124.37, 122.29, 121.43, 115.93, 113.87, 70.98, 42.25, 27.83. LC-MS (ESI), *m/z*:322 $[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{19}H_{20}N_3O_2$ $(M+H)^+$: 322.1550; Found: 322.1554.

4.1.4.8. Tert-butyl (S)-(1-(8-(2-(benzylamino)-2-oxoethoxy)quinolin-2-yl)pyrrolidine- 3-yl)carbamate ***1ah***. According to the general procedure, employing **11** and *(S)*-3-(boc-amino)pyrrolidine afforded compound **1ah** as an off-white solid, 49% yield, mp: 111–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 7.0 Hz, 1H), 7.30 (s, 1H), 7.28–7.24 (m, 2H), 7.17 (s, 4H), 6.67 (d, J = 9.0 Hz, 1H), 4.87 (s, 2H), 4.59–4.51 (m, 2H), 4.25 (s, 1H), 3.62 (s, 1H), 3.42 (s, 2H), 3.23 (s, 1H), 2.13 (s, 1H), 1.90–1.70 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.43, 155.75, 155.08, 152.24, 140.51, 139.30, 137.60, 131.98, 129.13, 128.68, 127.62, 127.27, 122.37, 115.98, 111.33, 78.34, 70.93, 52.45, 50.24, 45.18, 42.32, 30.49, 28.72. LC-MS (ESI), *m/z*:477 $[M+H]^+$. HRMS-ESI (*m/z*): Calcd. for $C_{27}H_{33}N_4O_4$ $(M+H)^+$: 477.2497; Found: 477.2516.

4.1.4.9. Tert-butyl (R)-(1-(8-(2-(benzylamino)-2-oxoethoxy)quinoline-2-yl)pyrrolidine- 3-yl) carbamate ***1ai***. According to the general procedure, employing **11** and *(R)*-3-(boc-amino)pyrrolidine afforded compound **1ai** as an off-white solid, 55% yield, mp: 112–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.35

(d, J = 7.0 Hz, 1H), 7.30 (s, 1H), 7.28–7.23 (m, 2H), 7.17 (s, 4H), 6.67 (d, J = 9.0 Hz, 1H), 4.87 (s, 2H), 4.61–4.48 (m, 2H), 4.24 (s, 1H), 3.62 (d, J = 10.5 Hz, 1H), 3.42 (s, 2H), 3.23 (s, 1H), 2.13 (s, 1H), 1.90–1.66 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.43, 155.75, 155.08, 152.25, 140.51, 139.30, 137.60, 131.97, 129.13, 128.67, 127.62, 127.26, 122.37, 115.99, 111.33, 78.34, 70.94, 52.46, 50.24, 45.18, 42.33, 30.49, 28.72. LC-MS (ESI), m/z:477[M+H]$^+$. HRMS-ESI (m/z): Calcd. for $C_{27}H_{33}N_4O_4$ (M + H)$^+$: 477.2497; Found: 477.2495.

4.2. Viruses and cells

Green Fluorescent Protein expressing recombinant RSV (RSV-mGFP; kindly provided by Prof. Jean-Francois Eleouet, Unite de Virologie et Immunologie Moleculaires (UR892), INRA, Jouy-en-Josas, France) and wild type subgroup A RSV Long strain (wtRSV, kindly provided by Prof. Y. Qian, Capital Institute of Pediatrics, Beijing, China) were propagated in HEp-2 cells (ATCC, Rockefeller, MD, USA) in DMEM (Gibco BRL, Gaithersburg, MD, USA) supplemented with 2% fetal bovine serum (FBS, Hyclone, Logan, UT, USA), L-glutamine (2 mmol/L), penicillin G (40 U/ml), streptomycin (100 μg/ml), and 0.2% sodium bicarbonate. RSV-mGFP and wtRSV were purified by sucrose ultracentrifugation, titrated for infectivity by immunoplaque assay, and expressed as plaque-forming units (pfu) per ml. HEK293T-Gluc cells were generated by transfection of plasmid DNA pLenti6-Gluc constitutively expressing the negative-strand RNA of Gaussia luciferase (Gluc) gene, that is converted into the positive strand upon IAV infection, and expresses the Gluc enzyme. A cell-based high-throughput approach to identify inhibitors of influenza A virus.

4.3. Cytotoxicity assay

Method 1 (for RSV): All compounds were individually subjected to cytotoxicity assay with MTS method. HEp-2 cells were plated in 96-well plates, and infected with virus alone or together with the test compound after 24 h. Following incubation for 48 h, 20 μl of 2 mg/ml MTS (Promega, Madison, WI, USA) was added to 96-well plates, and cells were further incubated for 3 h at 37 °C in a 5% CO_2 incubator. After shaking the plate for 10 s, absorbance was measured with a microplate reader (Tecan, Mannedorf, Switzerland) at a wavelength of 490 nm. Cells in the mock-treated control were left uninfected by virus or infected but untreated with the test compound. Cell activity was set as 100%.

Method 2 (for IAV): Cell viability was evaluated by cell counting kit-8 (CCK-8) assay. Briefly, 293T cells were cultured in a 96-well plate and incubated with compounds. Six concentrations of each compound, ranging from 12.5 μM to 200 μM, were used to treat cells for 48 h. Cells cultured in DMSO only were used as the control. After a 48-h incubation, 10 μL CCK-8 solution was added to each well and incubated for an additional 1 h at 37 °C. Optical density (OD) of each well at 450 nm was recorded on a Microplate Reader (Thermo, Varioskan Flash).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81703366), CAMS Innovation Fund for Medical Sciences (Nos. 2016-I2M-1–011, 2016-I2M-3–014, and 2017-I2M-3–019) and National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (No. 2019ZX09201001-003).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2021.113208.

Abbreviations

RSV	respiratory syncytial virus
IAV	influenza A virus
BXM	baloxavir marboxil
CEN	cap-dependent endonuclease
SAR	structure-activity relationship
HBTU	O-Benzotriazole-N,N,N′,N′-tetramethyl-uronium-hexafluorophosphate
DIPEA	N,N-diisopropylethylamine

References

[1] E. De Clercq, G. Li, Approved antiviral drugs over the past 50 years, Clin. Microbiol. Rev. 29 (2016) 695–747.
[2] A.T. Borchers, C. Chang, M.E. Gershwin, L.J. Gershwin, Respiratory syncytial virus-a comprehensive review, Clin. Rev. Allergy Immunol. 45 (2013) 331–379.
[3] C.B. Hall, The burgeoning burden of respiratory syncytial virus among children, Infect. Disord. - Drug Targets 12 (2012) 92–97.
[4] E.E. Walsh, A.R. Falsey, Respiratory syncytial virus infection in adult populations, Infect. Disord. - Drug Targets 12 (2012) 98–102.
[5] The Impact-RSV Study Group, Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants, Pediatrics 102 (1998) 531–537.
[6] K. Ventre, A.G. Randolph, Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children, Cochrane Database Syst. Rev. 5 (2010), CD000181.
[7] H.W. Li, M. Li, R.Y. Xu, S.X. Wang, Y.M. Zhang, L.H. Zhang, D.M. Zhou, S.L. Xiao, Synthesis, structure activity relationship and in vitro anti-influenza virus activity of novel polyphenol-pentacyclic triterpene conjugates, Eur. J. Med. Chem. 163 (2019) 560–568.
[8] Y. Wu, Y. Wu, B. Tefsen, Y. Shi, G.F. Gao, Bat-derived influenza-like viruses H17N10 and H18N11, Trends Microbiol. 22 (2014) 183–191.
[9] F. Carrat, A. Flahault, Influenza vaccine: the challenge of antigenic drift, Vaccine 25 (2007) 6852–6862.
[10] L. Zhou, Y. Tan, M. Kang, F.Q. Liu, R.Q. Ren, Y.L. Wang, T. Chen, Y.P. Yang, C. Li, J. Wu, H.J. Zhang, D. Li, C.M. Greene, S.Z. Zhou, A.D. Iuliano, F. Havers, D.X. Ni, D.Y. Wang, Z.J. Feng, T.M. Uyeki, Q. Li, Preliminary epidemiology of human infections with highly pathogenic avian influenza A(H7N9) virus, China, 2017, Emerg. Infect. Dis. 23 (2017) 1355–1359.
[11] World Health Organization Website, Influenza (Seasonal): Fact Sheet, 2018. http://cdrwww.who.int/mediacentre/factsheets/fs211/en/.
[12] H. Ju, J. Zhang, B. Huang, D. Kang, B. Huang, X. Liu, P. Zhan, Inhibitors of influenza virus polymerase acidic (PA) endonuclease: contemporary developments and perspectives, J. Med. Chem. 60 (2017) 3533–3551.
[13] E.J. Mifsud, F.G. Hayden, A.C. Hurt, Antivirals targeting the polymerase complex of influenza viruses, Antivir. Res. 169 (2019) 104545.
[14] Y. Furuta, B.B. Gowen, K. Takahashi, K. Shiraki, D.F. Smee, D.L. Barnard, Favipiravir (T-705), a novel viral RNA polymerase inhibitor, Antivir. Res. 100 (2013) 446–454.
[15] S. LlabrÃ©s, J. JuÃ¡rez-JimÃ©nez, M. Masetti, R. Leiva, S. VÃ¡zquez, S. Gazzarrini, A. Moroni, A. Cavalli, F.J. Luque, Mechanism of the pseudoirreversible binding of amantadine to the M2 proton channel, J. Am. Chem. Soc. 138 (2016) 15345–15358.
[16] R.M. Pielak, K. Oxenoid, J.J. Chou, Structural investigation of rimantadine inhibition of the AM2-BM2 chimera channel of influenza viruses, Structure 19 (2011) 1655–1663.
[17] L. Naesens, A. Stevaert, E. Vanderlinden, Antiviral therapies on the horizon for influenza, Curr. Opin. Pharmacol. 30 (2016) 106–115.
[18] A.C. Hurt, H.T. Ho, I. Barr, Resistance to anti-influenza drugs: adamantanes and neuraminidase inhibitors, Expert Rev. Anti Infect. Ther. 4 (2006) 795–805.
[19] T.G. Sheu, V.M. Deyde, M. Okomo-Adhiambo, R.J. Garten, X. Xu, R.A. Bright, E.N. Butler, T.R. Wallis, A.I. Klimov, L.V. Gubareva, Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008, Antimicrob. Agents Chemother. 52 (2008) 3284–3292.
[20] K. Bozorov, J.Y. Zhao, L.F. Nie, H.R. Ma, K. Bobakulov, R. Hu, N. Rustamova, G.Z. Huang, T. Efferthd, H.A. Aisa, Synthesis and in vitro biological evaluation of novel diaminothiophene scaffolds as antitumor and antiinfluenza virus

agents, RSC Adv. 7 (2017) 31417–31427.
[21] J. Xiong, J.J. Wang, G.P. Hu, W.L. Zhao, J.Q. Li, Design, synthesis and biological evaluation of novel, orally bioavailable pyrimidine-fused heterocycles as influenza PB2 inhibitors, Eur. J. Med. Chem. 162 (2019) 249–265.
[22] M.J. Vincent, E. Bergeron, S. Benjannet, B.R. Erickson, P.E. Rollin, T.G. Ksiazek, N.G. Seidah, S.T. Nichol, Chloroquine is a potent inhibitor of SARS coronavirus infection and spread, Virol. J. 2 (2005) 69.
[23] F. Touret, X. de Lamballerie, Of chloroquine and COVID-19, Antivir. Res. 177 (2020) 104762.
[24] X.F. Zheng, C.G. Liang, L.S. Wang, B.X. Wang, Y.F. Liu, S. Feng, J.Z. Wu, L. Gao, L.C. Feng, L. Chen, T. Guo, H.C. Shen, H.Y. Yun, Discovery of benzoazepine-quinoline (baq) derivatives as novel, potent, orally bioavailable respiratory syncytial virus fusion inhibitors, J. Med. Chem. 61 (2018) 10228–10241.
[25] G. Barbosa-Lima, A.M. Moraes, A.D.S. Araújo, E.T. da Silva, C.S. de Freitas, Y.R. Vieira, A. Marttorelli, J.C. Neto, P.T. Bozza, M.V.N. de Souza, T.M.L. Souza, 2,8-Bis(trifluoromethyl) quinoline analogs show improved anti-Zika virus activity, compared to mefloquine, Eur. J. Med. Chem. 127 (2017) 334–340.
[26] J.M. Rolain, P. Colson, D. Raoult, Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century, Int. J. Antimicrob. Agents 30 (2007) 297–308.