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Review

Progress of small molecular inhibitors in the development of anti-influenza virus agents

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Abstract

The influenza pandemic is a major threat to human health, and highly aggressive strains such as H1N1, H5N1 and H7N9 have emphasized the need for therapeutic strategies to combat these pathogens. Influenza anti-viral agents, especially active small molecular inhibitors play important roles in controlling pandemics while vaccines are developed. Currently, only a few drugs, which function as influenza neuraminidase (NA) inhibitors and M2 ion channel protein inhibitors, are approved in clinical. However, the acquired resistance against current anti-influenza drugs and the emerging mutations of influenza virus itself remain the major challenging unmet medical needs for influenza treatment. It is highly desirable to identify novel anti-influenza agents. This paper reviews the progress of small molecular inhibitors act as antiviral agents, which include hemagglutinin (HA) inhibitors, RNA-dependent RNA polymerase (RdRp) inhibitors, NA inhibitors and M2 ion channel protein inhibitors etc. Moreover, we also summarize new, recently reported potential targets and discuss strategies for the development of new anti-influenza virus drugs.

Key words: anti-influenza virus agent, hemagglutinin inhibitors, RNA-dependent RNA polymerase inhibitors, neuraminidase inhibitors, M2 ion channel protein inhibitors.

Introduction

The influenza virus continues to threaten public health because of its high morbidity and mortality rates despite the efforts and success of antiviral research (1-3). According to the World Health Organization (WHO), seasonal influenza virus epidemics result in the infection of 3-5 million people and 250,000 to 500,000 deaths worldwide (4). In recent years, the emergence of highly aggressive virus strains such as H1N1, H5N1, and H7N9 has reemphasized the need for therapeutic strategies to overcome these pathogens (5). Vaccines and antiviral agents are essential for mitigating the influence of the influenza virus (6, 7). Due to the frequent variation in the influenza virus, anti-influenza agents seem to be more effective at preventing the highly contagious infection with the virus and at treating disease epidemics.

Influenza pandemics are caused by the influenza virus, a negative-sense single-stranded member of the Orthomyxoviridae family of RNA viruses (8). Influenza virus could be classified as one of three distinct subtypes (influenza A, influenza B, or influenza C) depending on its nucleoproteins and the antigen determinants of its matrix proteins. Influenza A and influenza B appear to cause highly infectious diseases, while influenza C does not seem to cause significant disease (1). However, pandemic outbreaks are caused by influenza A viruses. Therefore, much

more attention has been paid to the influenza A viruses.

The structure of the influenza virus contains three motifs (**Figure 1**): the core, the matrix protein and the viral envelope (9). Influenza A virus was made up by proteins encoded by eight segments of negative-strand RNA (8, 10). These proteins include hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), RNA polymerase (PA, PB1, PB2), matrix protein 1 (M1), proton channel protein (M2), non-structural protein 1 (NS1) and nuclear export protein (NEP, NS2) (8, 11). Additionally, some proteins exist in particular strains were identified recently, such as PB1-F2 (12), PB1-N40 (10), and PA-X (13). Moreover, some novel proteins have been identified recently (14).

Depending on the differences of the subtypes of 18 HA (H1-H18) and 11 NA (N1-N11), influenza A viruses can be classified into 162 subtypes (15).

The life cycle of the influenza virus is a complex biological process and can be divided into the following steps (**Figure 2**): (i) attachment of the virion to the cell surface (receptor binding); (ii) endosomal internalization of the virus into cell (endocytosis and endocytosis); (iii) uncoating, cytoplasmic transport and nuclear import of viral ribonucleoproteins (vRNPs); (iv) transcription and replication of the viral RNAs; (v) nuclear exportation and protein synthesis; (vi) viral progeny assembly, budding and release from the cell membrane.

Viral proteins and host cellular proteins involved in each step of the life cycle of virus infection are attractive target to combat influenza virus infections (8, 16, 17).

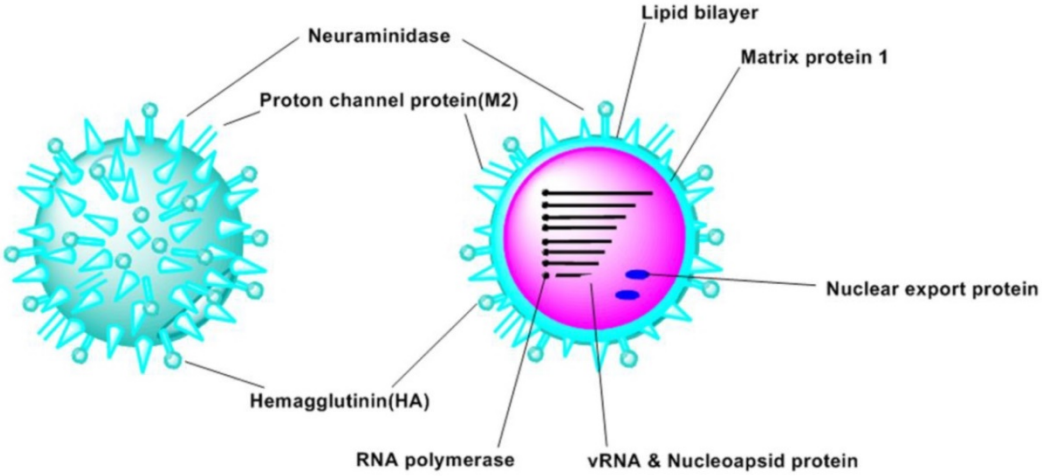

Figure 1. Schematic views of the structure of influenza A virus.

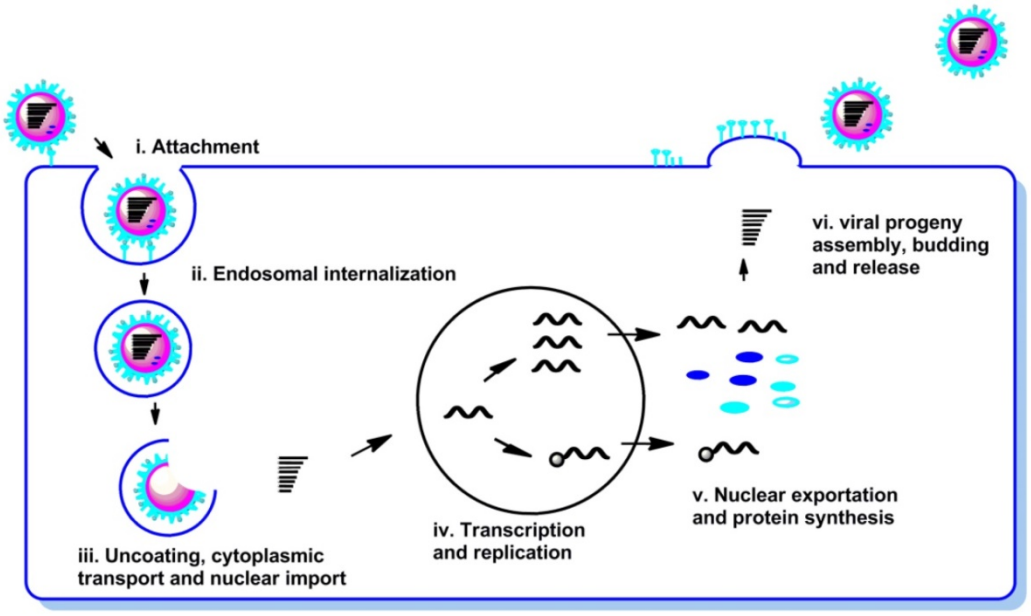

Figure 2. Schematic representation of the life cycle of influenza virus.

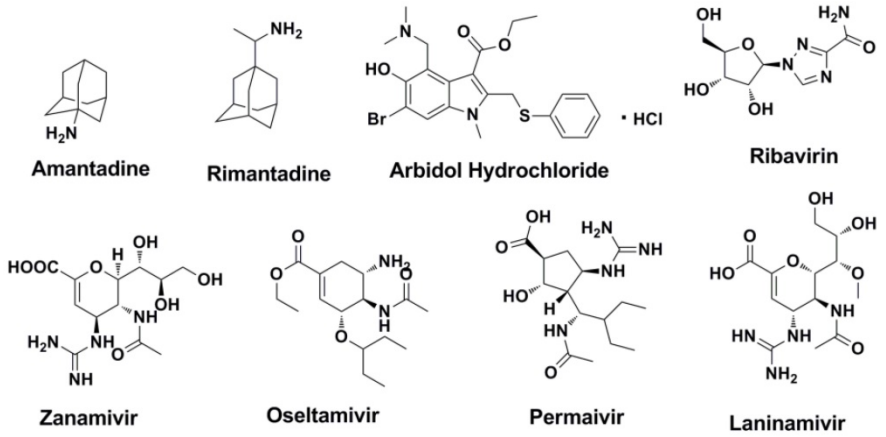

Figure 3. Structures of currently available licensed anti-influenza drugs.

At present, only a few drugs that function as influenza NA inhibitors, M2 ion channel protein inhibitors, RNA-dependent RNA polymerase inhibitors and protease inhibitors are used in clinical. Structures of currently available licensed anti-influenza drugs were shown in **Figure 3**.

The emergence of influenza virus mutations and acquired resistance are extremely influential in driving the development of new anti-influenza agents against possible future influenza epidemics. Small molecular inhibitors (molecular weight less than 1000) are powerful tools to fight against influenza virus. Besides small molecular inhibitors, peptides (Entry Block-peptide (EB-peptide) (18, 19), FluPep (FP) peptides (20) , NDFRSKT (21, 22) etc.), proteins (Hepatocyte growth factor activator inhibitor 2 (23), Ulinastatin (23-25) and Fludase (26-28)), monoclonal antibodies (29) , Nanoparticles (30-33) and other types of anti-viral drugs are effective in influenza virus infection (those agents are out of the scope of this article). According to the target of the antiviral agent, research on anti-influenza virus agents can currently be categorized into two fields: agents that target functional proteins of the virus itself and agents that target potential sites of the host cells.

1. Agents targeting functional proteins of the virus itself

The HA protein facilitates viral binding to receptors on host cells receptors and the fusion process. Viral RNA replication and transcription is carried out by the nucleoprotein (NP) and three polymerase subunits (PB2, PB1 and PA). The M2 protein is involved in uncoating and maturation of the virus. The NA protein is essential for the release of the virus from infected cells. Therefore, the functional proteins described above are attractive targets for antiviral research.

1.1 Entry inhibitors

Antiviral compounds designed (or discovered) to interrupt the attachment and entry course of the virus were named entry inhibitors (34). Extracted from nature produce from Traditional Chinese Medicine (TCM) licorice, triterpenoids derivatives showed antiviral activities (35-40). Glycyrrhizic acid (or named glycyrrhizin) (41) and glycyrrhetinic acid (42) have been proved to be effective to interrupt the attachment and entry course of the influenza virus **(Figure 4)**.

Glycyrrhizin exhibited broad spectrum inhibitory activity and showed the most potent inhibitory activity against the replication of H3N2, H5N1 etc (43). Saponins and uralsaponins M-Y (**Figure 4**) showed anti-influenza activities in recent studies (44). Uralsaponins M exhibited inhibitory activities against influenza virus A/WSN/33 H1N1 in MDCK cell lines with IC_{50} value of 48.0 μM (44).

As a negatively charged sulphated polysaccharide, Dextran sulphate (DS, **Figure 4**) inhibit the attachment and entry course as well as the HA-dependent (45, 46) and NA-dependent (47) fusion course (strictly speaking, DS is not a small molecular). Silymarin (**Figure 4**) (48), extract from milk thistle seeds, showed activity against influenza. Its main component silibinin and derivatives can also regulate autophagy course. As a multi-target natural product, curcumin can also inhibit the virus entry course and HA activity (EC_{50} was approximately 0.47 μM for inhibition of influenza virus, Plaque Reduction Assay) (49-51). Lysosomotropic agents (such as Concanamycin A, Bafilomycin A1, Chloroquine etc.), exhibit their anti-influenza activities depending on the pH value of the intracellular environment (52-57).

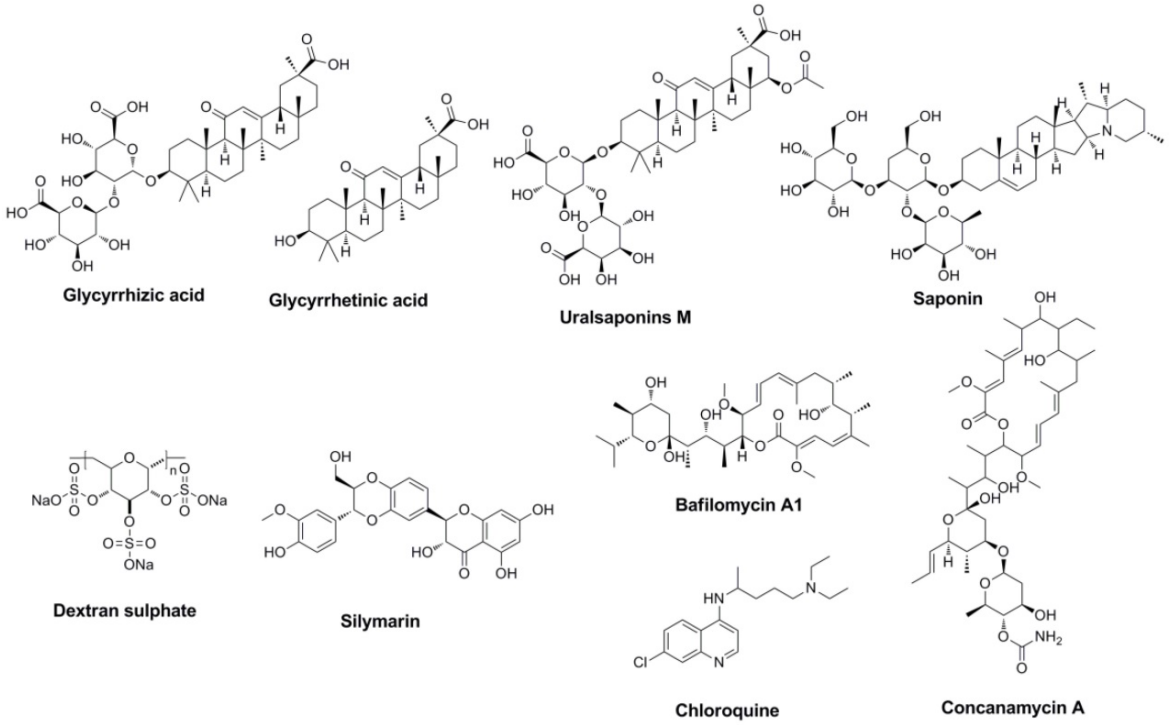

Figure 4. Structures of representative entry inhibitors.

1.2 Hemagglutinin (HA) inhibitors

HA is encoded by the vRNAs and is composed of three identical structural subunits (1). These subunits have two important functions in linkage and the internalization trigger: first, HA can provide a link between the virus and the surface of target host cells (58-60); and second, HA triggers the internalization of the virus through the fusion of the viral envelope and the endosomal membrane of the host. Both HA and NA recognize N-acetylneuraminic acid (Neu5Ac, also called sialic acid), a typical terminal unit of glycoconjugates attached to the membranes of cells in the upper respiratory tract and lungs (1), to facility its function.

HA is formed via the proteolytic cleavage of the precursor protein HA0 into either HA1 or HA2, and the inhibitors of HA can be classified into two different subtypes. The first type of inhibitor blocks the association between HA1 and the neuraminic acid (Neu) receptors on the surface of the target host cells. The second type of inhibitor, such as BMY-27709 (61, 62) and stachyflin (63-65), interrupts the HA2-mediated fusion process (**Figure 7**). This second type of inhibitor can inhibit the conformational transition of HA2 that is induced by lower pH values.

Extracted from cotton plant in 1970s, a natural phenolic aldehyde named Gossypol (**Figure 6**) was found to be effective against pneumonia caused by influenza virus (66-69). Further studies found that other natural products (or its derivatives) such as Rutin (70, 71), Quercetin (71-74), Xylopine (71, 75) and Theaflavins (76, 77) are HA inhibitors that interacts with HA (**Figure 6**).

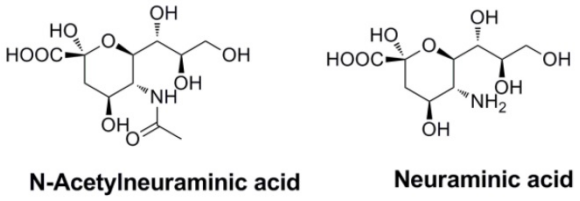

Figure 5. Structures of N-acetylneuraminic acid and neuraminic acid.

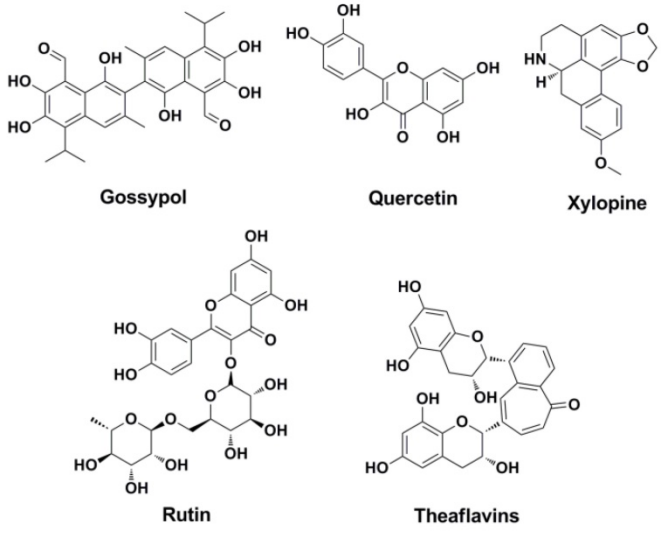

Figure 6. Structures of typical natural products as HA inhibitors.

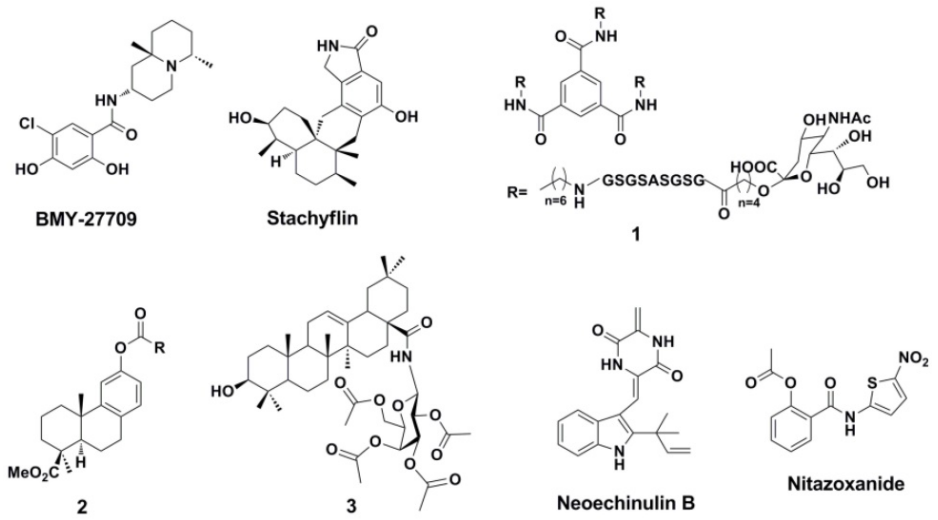

Figure 7. Structures of newly developed HA inhibitors.

BMY-27709, contains a salicylamide scaffold and has been identified as specific to the influenza A virus (with IC_{50} values of 3-8 mM in a multicycle replication assay for A/WSN/33 virus) (61). BMY-27709 was found to inhibit the H1 and H2 viruses (though it is inactive against H3 virus) in the early stage of infection. Further study has indicated that BMY-27709 blocks the HA-mediated fusion process (62). Stachyflin (**Figure 7**) is a HA inhibitor that is similar to BMY-27709 in that it has activity against the H1 and H2 influenza A viruses (64). Experiments have suggested that Stachyflin blocks the HA-mediated cell fusion process by inhibiting the conformational transition of the HA protein (64, 65).

It is interesting that a trivalent glycopeptide mimetic (compound **1, Figure 7**) displayed inhibitory activity against HA (H5) of avian influenza (inhibitory constant (Ki) = 15 μM and compound **1** is not a small molecular but this compound cannot simply be subdivided into peptide either) (2). The follow-up work carried out by Zhao et al found that a series of podocarpic acid derivatives (compound **2, Figure 7**) exhibited potent activities (EC_{50} = 140-640 nM) against a cell-line adapted influenza virus (A/Puerto Rico/8/34, PR8, an oseltamivir and amantadine resist H1N1 strain) infection of MDCK (Madin-Darby canine kidney) cells (78). Natural product pentacyclic triterpenoids (compound **3, Figure 7**) exhibited inhibitory against influenza viruses, which were comparable to or even more potent than that of oseltamivir (79). Compound 3 was effective against the A/HuNan-ZhuHui/1222/2010 H3N2 strain (amantadine and ribavirin resistant), the A/LiaoNing-ZhenXing/ 1109/2010 H1N1 strain (oseltamivir-resistant), and even the influenza B/ShenZhen/155/2005, with EC_{50} values of 3.18, 6.58, and 2.80 μM (MDCK cell- based Cytopathic effect reduction assay, CPE Assay). Obtained from marine-derived fungus Eurotium rubrum, a class of novel prenylated indole diketopiperazine alkaloids displayed potent inhibition against H1N1 virus including oseltamivir and amantadine-resistant clinical isolates (80). The indole alkaloids (such as Neoechinulin B) can disrupt the interaction between the virus and host cells through binging to influenza envelope HA (80). The EC_{50} valuses of Neoechinulin B against A/LiaoNing-ZhenXing/1109/2010 H1N1, A/HuNan-ZhuHui/1222/2010 H3N2 and A/WSN/33 H1N1 were 16.89, 22.22 and 27.4 μM, respectively (MDCK cell- based CPE Assay).

Thiazolides such as Nitazoxanide (**Figure 7**) are powerful broad-spectrum antiviral drugs by blocking the maturation of viral HA, which made them be active against influenza viruses (81-86). The IC_{50} valuses of Nitazoxanide against influenza A/WSN/1933 H1N1, A/Parma/24/2009 H1N1 (Oseltamivir-resistant), A/Parma/06/2007 H3N2 (amantadine-resistant), A/goose/Italy/296246/2003 H5N9 and A/turkey/Italy/RA5563/1999 H7N1 were 1.6, 1.9, 1.0, 3.2 and 1.6 μM, respectively (MDCK cell-based CPE assay).

1.3 NA inhibitors (NAIs)

NA (also called sialidase) is a viral enzyme that is made up of four identical subunits and is anchored to the membrane of the virus (87). NA plays a key role in the spreading of the virus. The terminal neuraminic acid residues of the glycoproteins of the newly formed virion progeny form glycosidic linkages with the neuraminic acid receptor on the host-cell surface; this glycosidic linkage is cleaved by NA, which thereby assists in the release of the virion progeny from the infected cells (88, 89). Therefore NA is an attractive target for anti-influenza research, and

inhibitors of NA containing a Neu core have attracted much attention (90-92).

Meindl et al synthesized FANA (93, 94) and DANA (Neu5Ac2en)(94, 95), which are analogues of sialic acid (**Figure 8**). However, further study indicated that DANA has limited activity and failed as a clinical treatment of influenza (95-97). Von Itzstein and colleagues (98) modified the structure of DANA to synthesize the novel NA inhibitor Zanamivir (**Figure 8**). Zanamivir was effective against influenza A/(Singapore/1/57 and B/Victoria/102/85 virus with IC_{50} values of 14 nM and 5 nM, respectively (MDCK cell-based Plaque Reduction Assay). Although the oral bioavailability of Zanamivir is very low (2%-3%), the FDA approved it in 1999 as the first NA inhibitor agent (formulated for oral inhalation).

Based on the structure of Zanamivir and the 3-dimensional structure of Zanamivir and influenza-virus NA (subtype N9) (99) , Kim et al (100) synthesized Oseltamivir (**Figure 8**), which has enhanced oral bioavailability. The FDA also approved Oseltamivir in 1999, and it is the most popular NA inhibitor in the clinic at present. The activities of Oseltamivir carboxylate against representative N3-N9 NAs with IC_{50}s range from 0.3 nM to 1.5 nM (Neuraminidase Enzyme Assay). More importantly, Zanamivir and Oseltamivir are effective against amantadane resistant strains.

Peramivir (101) and Laninamivir (102, 103) are also used as NA inhibitors and currently licensed in Asian countris (**Figure 8**). Peramivir is only administered intravenously because of its poor bioavailability (104). Laninamivir showed potent NA inhibitory activities against 11 strains of H1N1 viruses, 15 strains of H3N2, 23 strains of B viruses with IC_{50} valuses range 1.29-5.97 nM, 7.09-38.8 nM and 10.4-31.4 nM, respectively (Enzymatic assays). Laninamivir (also formulated for oral inhalation) is a long-term NA inhibitor, and it appears to be effective for patients with Oseltamivir resistance (94, 105-107). The suggested treatment usage of laninamivir (Japan) is beneficial when patients confer resistance to oseltamivir (94, 106, 107).

The recent progress in researching NA inhibitors has mainly focused on the structure modification/optimization of Zanamivir and Oseltamivir, both of which are similar to the Neu analogues (compounds **4-9**, **Figure 8**) (108-115).

The development of irreversible inhibitors is an attractive strategy for overcoming drug resistance. Designed and synthesized by Kim et al. (116), those compounds (represented by compound **10, Figure 8**) could form transient covalent intermediates with Tyr406 located at the catalytic domain of NA, thereby gaining potent broad-spectrum inhibitory activity against drug-resistant strains. Furthermore, those compounds exhibited equivalent or better drug efficacies in animal experiments.

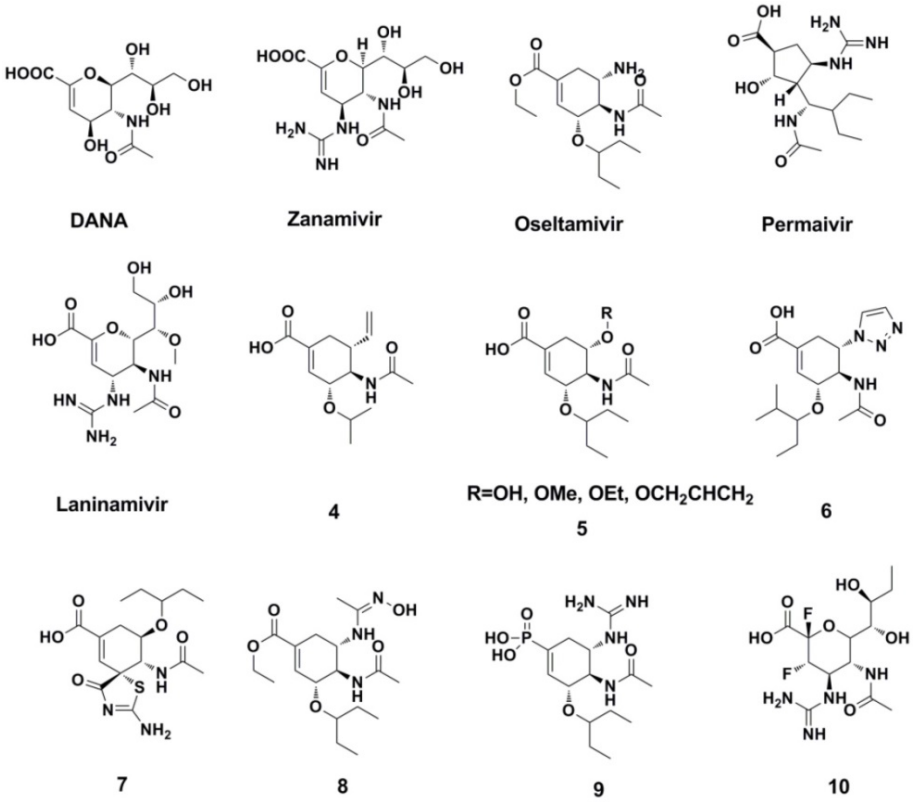

Figure 8. Structures of representative NAIs.

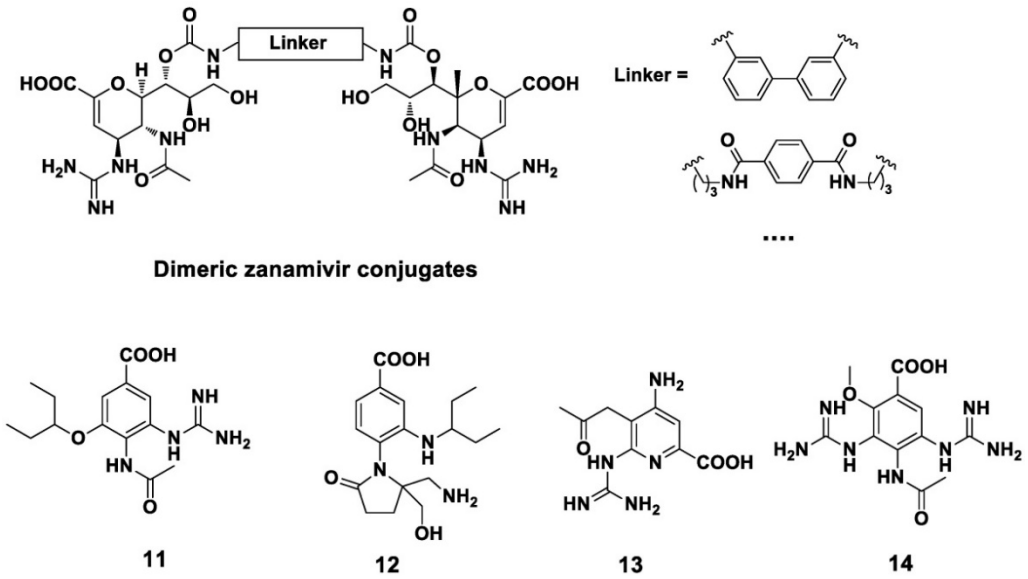

Figure 9. Structures of dimeric zanamivir conjugates and benzoic acid derivatives.

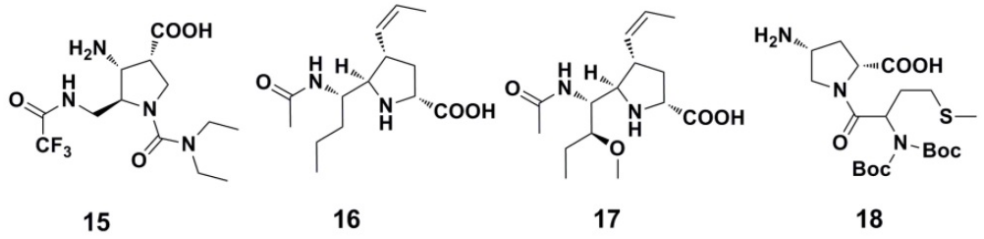

Figure 10. Structures of pyrrolidine derivatives as NAIs.

Remarkably, dimeric (or tethered) NA inhibitors developed by Tucker and co-workers are prospective for the clinical realization as anti-influenza agents (117-120). Dimeric zanamivir conjugates were synthesized and proved to be highly potent NA inhibitors **(Figure 9)** (120, 121). These dimeric compounds showed broad-spectrum activity and were 10-1000 fold more potent than that of zanamivir.

With the aim to find novel, potent NA inhibitor, benzoic acid derivatives (**Figure 9**) were developed in recent studies (122-125). However, the plane of the aromatic ring may limit the orientation of the substituent group, resulting in the poor activity of these benzoic acid derivatives. Pyrrolidine derivatives are also effective against the influenza A virus (**Figure 10**). Wang et al (126) found compound **15** showed anti-influenza activity (IC_{50} = 0.2 μM against NA A/Tokyo and 8 μM against NA B/Memphis, NA inhibition assay). Compound **16** (127) and compound **17** (128), showed anti-influenza activity against influenza A and influenza B, respectively. Compound **18,** as an analogue of L(-)-proline, showed inhibitory activity against NA from the influenza A virus (129).

Some natural products have also been found to possess anti-influenza activities in past few years (**Figure 11**). Ginkgetin-sialic acid conjugates (compound **19**) (130), significantly improved the survival rate of mice infected with the influenza virus. Flavanones and flavonoids (**Figure 11**, **20-23**) also showed potent NA inhibition (IC_{50} ranges 1.4-20 μM against NA, NA inhibition assay) (131-134). Isoscutellarein (compound **24**) and its derivatives are also active in cellular assays (EC_{50} = 20 μM against influenza A/Guizhou/54/89 H3N2, MDCK cell-based CPE assay) and animal models (135, 136).

A novel highly potent oral drug candidate AV5080 (**Figure 12**) exhibited subnanomolar activity against influenza virus NA *in vitro* (with IC_{50}s = 0.03 nM and 0.07 nM against NA of A/Duck/Minnesota/1525/1981 H5N1 and A/Perth/265/2009 H1N1 in NA enzyme based assays, respectively) (137). The N-substituted Oseltamivir analogues (compound **25, Figure 12**) displayed enhanced inhibition against NA from Oseltamivir-resistant and wild-type strains (138). Jin-Hyo Kim et al synthesized a series covalent NA inhibitors (represented by compound **26** and **27, Figure 12**) by introducing the strong electronegative fluorine atom at core-ring of Zanamivir and Oseltamivir (116); and these compounds showed excellent antiviral activity *in vitro*. Compound **27** showd IC_{50} values of 1 nM and 10 nM agaisnt

B/Perth/211/01 and A/Fukui/45/01 H3N2 in plaque size reduction assays, superior than those for Zanamivir (10 nM and 100 nM, respectively). These compounds also showd comparable inhibition levels in animal models (compared with Zanamivir) (116).

1.4 RNA-dependent RNA polymerase (RdRp) inhibitors

The RNA-dependent RNA polymerase (RdRp) of the influenza virus has been highly conserved among all strains and subtypes during evolution (139). Unlike mammals, the RdRp of the influenza virus exhibits activities of both replicases and endonucleases. During the early stages of infection, RdRp synthesizes mRNA using vRNA as a template. During the advanced stage of infection, as the conformation of RdRp changes, RdRp becomes responsible for the catalytic synthesis of cRNA and vRNA (140-143). RdRp was also named "3P-complex" because it is composed of three subunits (PA, PB1 and PB2). RdRp plays a critical role during the life cycle of the virus. Therefore, it has become a promising target for the development of anti-influenza drugs in recent years (144, 145). Based on the mechanism of the interactions berween inhibitors and polymerase, RdRp inhibitors can be easily subdivided into the following four subtypes (146, 147): (i) RdRp disrupting compounds, (ii) PB2 cab-binding (PB2-CBD) inhibitors, (iii) PA endonuclease inhibitors, (iv) PB1 or nucleoside analogue like inhibitors.

RdRp disrupting compounds: An attractive strategy for developing RdRp inhibitors appears to be interrupting the subunits interactions (the assembly course of the subunits in to a functional polymerase complex), and this strategy proves to be effective in recent studies. Figure **13** shows the structures of typical RdRP disrupting inhibitors (compounds **28-33**, **Figure 13**) (17, 148-153), and RdRp disrupting compounds also named prpotein-protein interaction inhibitors (PPI inhibitors) because of its interference/or inhibiton of the protein-protein interaction in the assembly course.

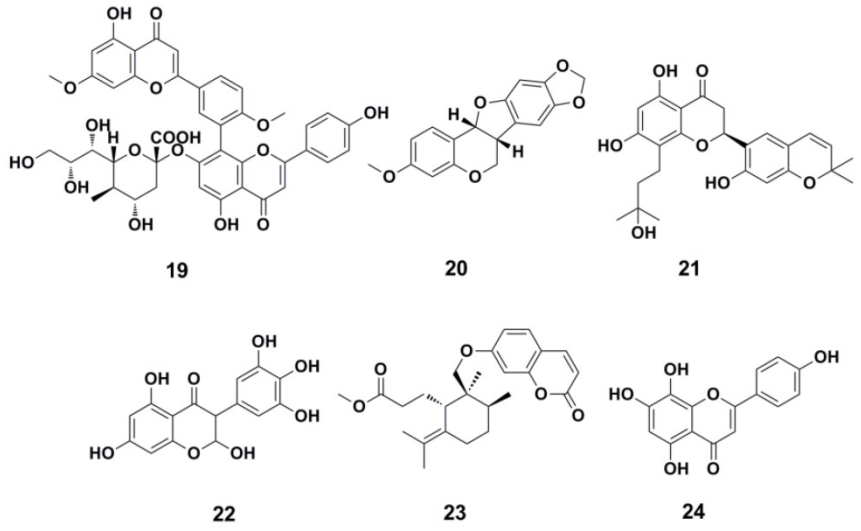

Figure 11. Structures of nature products as NAIs.

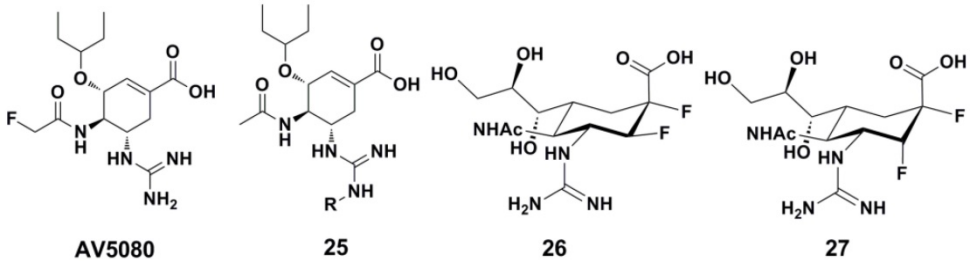

Figure 12. Structures of newly developed NAIs.

PB2 cab-binding inhibitors: The cap-binding activity resides in PB2 subunit was discovered more than 30 years ago (154, 155), but the binding mode of influenza A and B was revealed since the X-ray structure of the PB2 cap-binding domain was reported in 2008 (156). PB2-CBD as a drug target was validated by the clinical candidate VX-787 (94, 157-159) (**Figure 14**). As an azaindole based inhibitors, VX-787 was able to occupy the m^7GTP binding pocket in the PB2-CBD of influeza A (demonstrated by X-ray structure) (156). VX-787 displays potent antiviral activity against a widely range of influenza A virus strains in cellular assays (with EC_{50}s in nanomolar range), including amantadine- and NAI-resistant strains. Cap-3 and Cap-7 (**Figure 14**) were also cap-binding inhibitors and were reported recently by Roch et al (160). These two compounds can inhibit the transcription process in enzymatic assay and inhibit the virus replication process in cell experiments (with EC_{50}s range 1-9 μM).

PA endonuclease inhibitors: Another promising target in polymerase may be the conserved residues inside of the catalytic site of N-terminal domain of PA. This stragety was also validated since the introduction of AL-794 and S-033188 (structures undisclosed) as PA inhibitors into clinical trials (161). The challenge of the strategy is to achieve inhibitors consist of metal-chelating scaffolds to bind the divalent metal ion(s), and occupy the PA-Nter catalytic site. Many inhibitors of this type have been report so far, and these inhibitors have in common that they possess chelating motifs (147). These inhibitors include: EGCG (162, 163) and its aliphatic analogues (EGCG analogues also showed inhibitory activity against Neuraminidase) (164), N-hydroxamic acids and N-hydroxyimides (165), flutimide (166) and its aromatic analogues (167), tetramic acid derivatives (168), L-742,001 (169, 170), ANA-0 (171), polyphenolic catechins (162), phenethyl-phenylphthalimide analogues (172), macrocyclic bisbibenzyls (163, 173), pyrimidinoles (174), fullerenes (175), hydroxy-quinolinones (176), hydroxypyridinones (IC_{50} = 11 nM in Enzymic Assay, compound **34**) (177), hydroxypyridazinones (178), trihydroxy-phenyl-bearing compounds (compound **35** and **36**) (179-181), 2-hydroxy-benzamides(182), hydroxy-pyrimidinones (183), β-diketo acid and its bioisosteric compounds (184), thiosemicarbazones (183), bisdihydroxyindole-carboxamides (185), pyrido-piperazinediones (Endo-1) (160) and miscellaneous compounds (186). However, quite a number of these compounds showed in cell experiments, which is likely to be connected with the poor cellular uptake and/or insufficient anti-viral activity and selectivity. Structures of the representative inhibitors were shown in **Figure 14**.

Nucleoside and nucleobase analogue inhibitors: This subtype of RdRp inhibitors is likely to be most promising in anti-influenza drug development because of the following advances: low cytotoxicity, high resistance barrier and broad coverage of diverse RNA viruses (147).

Ribavirin (**Figure 14**) (187) and Favipiravir (188, 189) (also named T-705, **Figure 14**) are RdRp inhibitors that both have a nucleoside fragment. Ribavirin was approved as a broad-spectrum antiviral drug for years (190, 191) and Favipiravir has advanced to phase II clinical trials (USA) and phase III clinical trials (Japan). Ribavirin can influence the DNA/RNA synthesis of the host cell (192, 193) through a combination of several different mechanisms (147). Further research reveals that ribavirin and its analogues (5-azacytidine and 5-fluorouracil) are lethal mutagens of influenza virus (194).

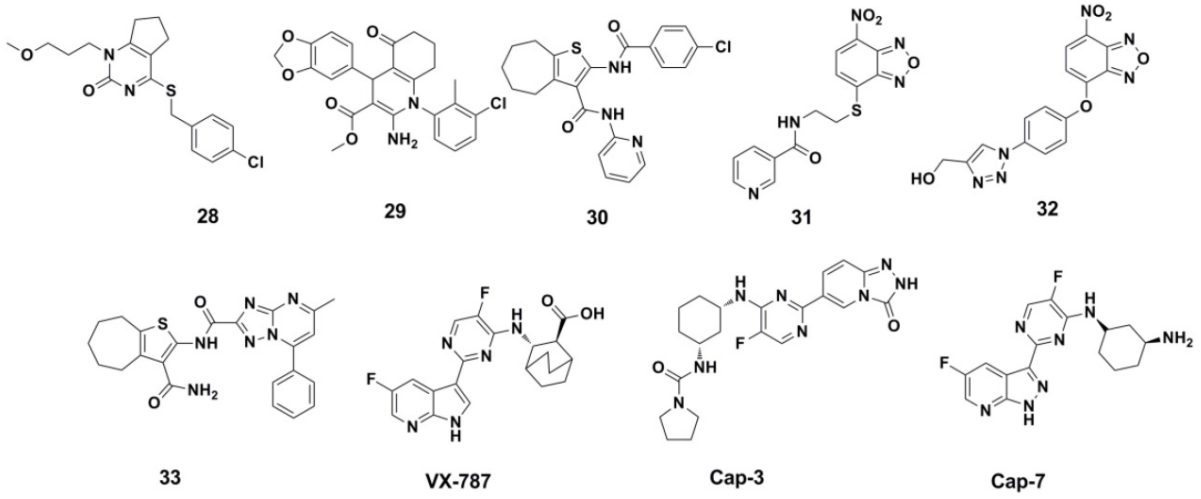

Figure 13. Structures of RdRp disrupting compounds and PB2 cab-binding inhibitors.

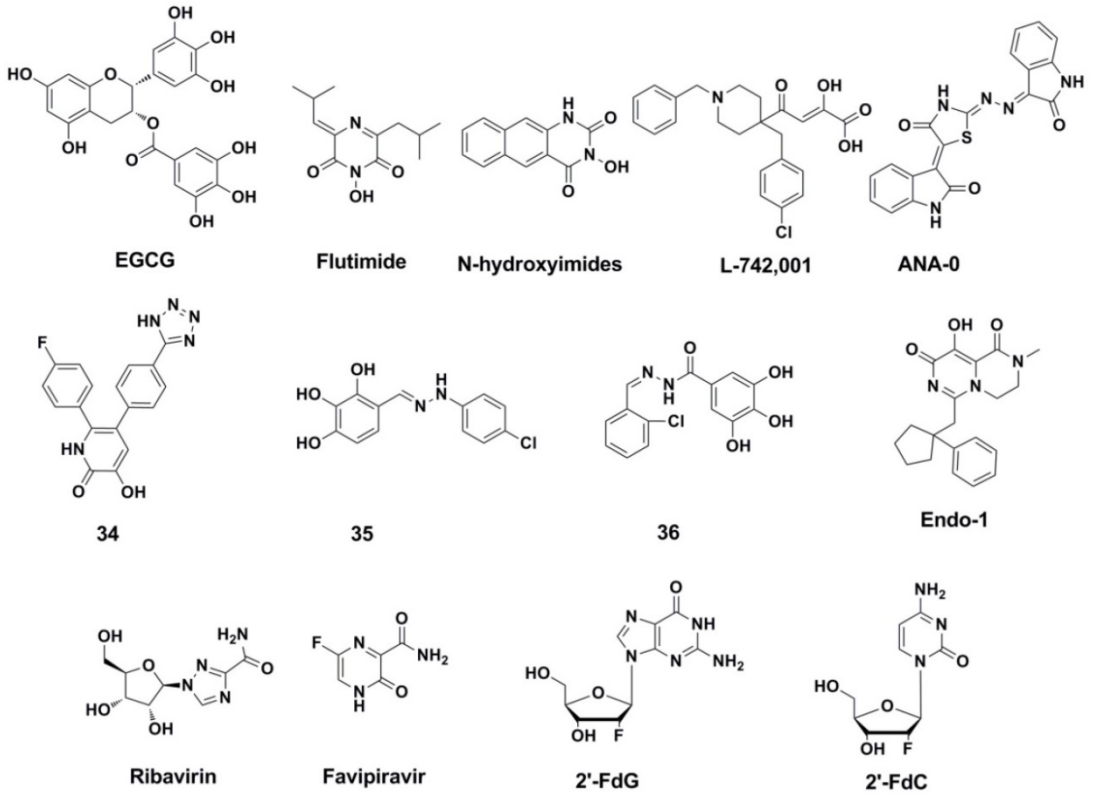

Figure 14. Structures of representative PA endonuclease inhibitor, Nucleoside and nucleobase analogue inhibitors.

As a nucleobase mimetic, Favipiravir and its analogues showed to be effective against strains that are resistant to NA inhibitors and M2 ion channel protein inhibitors (188, 195-199).

2′-Deoxy-2′-fluoroguanosine (2′-FdG) (200) and other nucleoside analogues (such as C-3′-modified analogues (201), 2′-substituted carba-nucleoside analogues (202), 6-methyl-7-substituted-7-deaza purine nucleoside analogues (203) etc.) were reported to posess anti-influenza activities against influenza A and B viruses. 2′-FdG can inhibit the polymerase complex through nonobligate chain termination. As a pyrimidine analogue of 2′-FdG, 2′-deoxy-2′-fluorocytidine (2′-FdC) seems more potent against various strains of influenza A and/or B *in vitro* and *in vivo* (204). Although these nucleoside analogues showed strong inhibitory activities, the clinical application was limited because the therapeutic window is too narrow (147).

1.5 Nucleocapsid protein (NP) inhibitors

NPs account for 30% of the total protein of the virus and, as a structural protein, form the virus ribonucleoprotein (vRNP) (205, 206). NP has multiple functions in the virus and is involved in replication, the formation of specificity to the host, and other activities (7, 207). Recent research has resulted in the discovery of some potential targets and inhibitors of NP (7, 148, 208-210). A study carried out by Ye and co-workers indicated that the tail loop-binding pocket in the influenza A virus NP could be a potential site for antiviral development. Kao et al (210) found a small molecular, nucleozin (NCZ, **Figure 15**), which may inhibit the infection caused by the H1N1, H3N2 and H5N1 strains as it can initiate the aggregation process of NP, blocking its nuclear accumulation (with EC_{50}s of 0.069 μM, 0.16 μM and 0.33 μM showd in MDCK cell-based Plaque Reduction Assay, respectively). Their work also proved that viral NP is a potential target for the development of anti-influenza drugs. Ke ding et al (211) replaced the isoxazole ring of nucleozin with triazole to obtain compound **37 (Figure 15)**, which showed enhanced activity against the replication of various H1N1, H3N2, H5N1 and H9N2 influenza A virus strains (with IC_{50}s ranges 0.15-12.4 μM, MDCK cell-based Anti-influenza Assay). Furthermore, compound **37** was also effective against strains that are resistant to amantadine (A/WSN/33, H1N1) and oseltamivir (A/WSN/1933 H1N1, 274Y).

Small molecules such as Cycloheximide (CHX, **Figure 15**) (212-214) and Naproxen **(Figure 15)** (215) were found to be effective against the functional polymerization of the NP monomers. Furthermore, a licensed drug named Ingavirin (approved in Russia, **Figure 15**) interacts with NP directly by interrupt transportation of newly synthesized NPs to the nucleus (173, 216-221).

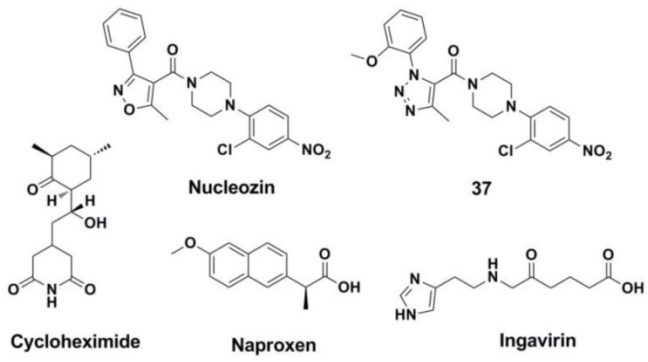

Figure 15. Structures of NP inhibitors.

1.6 M2 ion channel inhibitors

The M2 ion channel protein is a transmembrane protein that possesses the activities of typical ion channels (222-225). Influenza B lacks an M2 ion channel protein, but the B/M2 protein functions as an M2 ion channel protein during the assembly of the virus (225). The M2 and B/M2 proteins play important roles in the incorporation of the viral ribonucleoprotein (vRNP) complex into the virus during the assembly process.

Although the M2 inhibitors (Amantadine and Rimantadine) are firstly approved and recommend for use in clinical, but drug resistance has limited their clinical use. Most H1N1, H3N2 strains and virus B are resistant to Amantadanes, but the resistance to Zanamivir and Oseltamivir is very low. Furthermore, neurotoxic effects (such as confusion, disorientation, anxiety, jitteriness, etc.) caused by Amantadine are usually more common when the drug is used more than a week. Since the structure of M2 channel protein has been determined (226), developing more potent drugs against H1N1 influenza virus and solving the drug-resistant problem become promising (226-229).

M2 inhibitors can be classified as two groups based on the structure of the inhibitors (34). The first group includes Amantadine and Rimantadine (225) analogues (226, 230-234) (**Figure 16**, compounds **38-40).** Amantadine and compound **39** showed activities against influenza A H3N2 virus with IC_{50}s of 3.35 and 8.58 μM in a MDCK cell-based CPE Assay, respectively. The second group is non-adamantane derivatives and promising drugs (235, 236). Polyamines are effective against influenza virus (such as Spermine and Spermidine, **Figure 16**) (237, 238). This is because there is another binding site for polyamines at the M2 protein (significantly distinct from the Amantadine binding site) (239), and polyamines have attracted much attention for developing novel anti-influenza drugs (240, 241). Spiropiperidine and its derivatives (represented by compound **41** in **Figure 16**) are also effective against M2 protein and showed activities against amantadine-resistant viruses (34). Nature products such as pinanamine derivatives (compound **42** in **Figure 16**) also exhibit good anti-influenza activities (242). However, almost none of M2 inhibitors are effective against the influenza B virus (225).

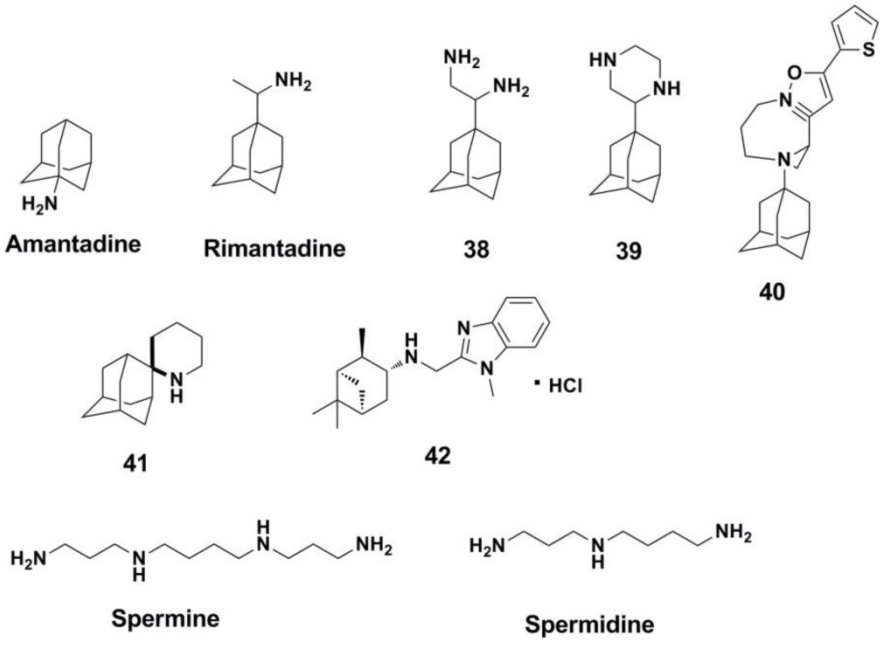

Figure 16. Structures of M2 ion channel inhibitors.

Mopyridone (**Figure 17**), a compound which was screened from a series of tetrahydro-2(1H)-pyrimidinone derivatives by Galabov et al in 1980s (243, 244), demonstrated to be a large scope anti-flu effect and large spectrum of influenza A1H1, AH2N2, AH3N3 and B strains *in vitro* and *in vivo* (245). What is particularly noteworthy is that this compound is the only anti-flu compound for which it was proved to have as a target M1 protein (246), and further research shows this compound with low acute toxicity in mice (247).

1.7 Arbidol hydrochloride

Developed by the Pharmaceutical Chemistry Research Center of the former Soviet union (248-251), arbidol hydrochloride (AH, **Figure 17**) was selected as a new antiviral drug for influenza infection in Russia and China (250, 251). AH is effective for the prophylaxis and treatment of influenza and other acute respiratory viral infections (ARVI) (250). AH inhibits viral entry into target cells and also stimulates the immune response (252). At the same time, AH has immunomodulatory activity, a capacity to induce interferons, and antioxidant properties. Although some studies from Russia and China have proved AH to be effective, it has not been approved for use in western countries.

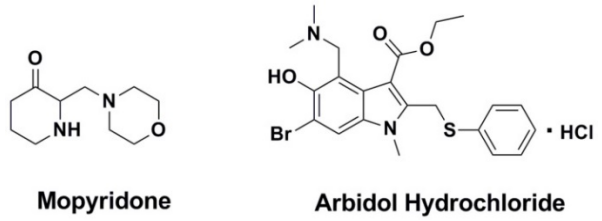

Figure 17. Structures of Mopyridone and Arbidol Hydrochloride.

2. Agents targeted at potential host sites

The potential targets for antiviral therapies include proteases, vacuolar-type proton-adenosine triphosphatases (V-ATPases), kinases, and other proteins. However, the effectiveness of inhibitors against these enzymes needs further improvements.

2.1 Protease inhibitors

The interaction between the host protease and the splice site of the viral precursor protein HA0 determines whether the species is infected with influenza and affects the virulence of the virus. For example, the splice site of HA0 in highly pathogenic avian influenza strains such as H5 and H7 can be easily be spliced by the widespread basic amino acid protease or PC6 serine protease, resulting in fatal systemic infection in birds (253, 254). In fact, known inhibitors such as nafamostat, Leupeptin (255), epsilon-aminocapronic acid (256), Camostat (257), Aprotinin (258) have been studied for years (**Figure 18**). Some of them (such as Camostat) have shown selective inhibition against the influenza A and influenza B viruses *in vitro* and *in vivo* (259).

2.2 V-ATPase inhibitors

The selective V-ATPase inhibitors may increase the internal pH of the prelysosome, thereby inhibiting the conformational transformation of HA from the unfused conformation to the fused conformation. This would result in the inhibition of replication during the course of the viral life cycle. It is interesting that four drugs used in the treatment of Parkinson's disease (NorakinR, ParkopanR, AntiparkinR and AkinetonR) all contain an adamantine scaffold that has shown inhibitory activity against the influenza A and influenza B viruses (260-262).

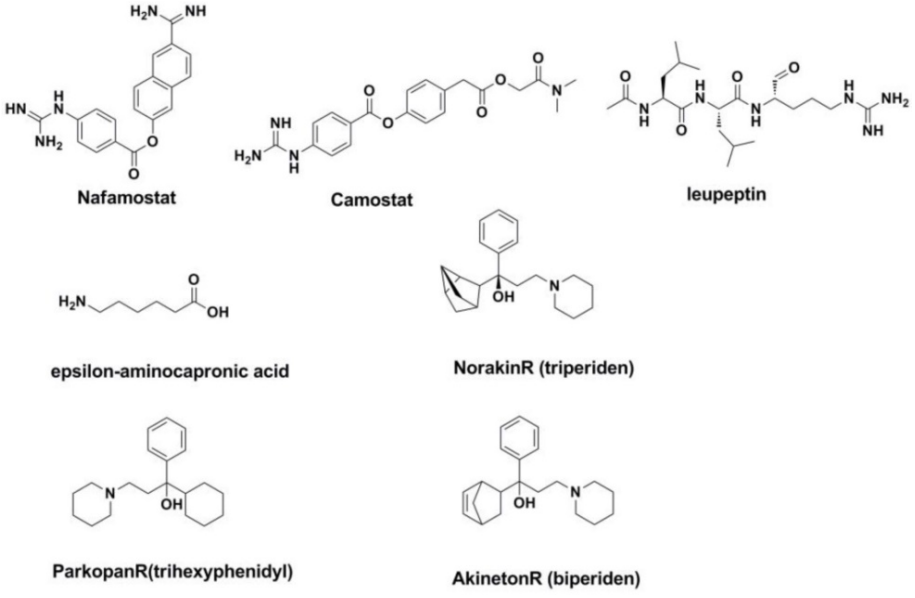

Figure 18. Structures of agents targeted at potential sites of host.

2.3 Anti-oxidants

Increasing evidence has indicated that the oxidation plays a major role in influenza virus life cycle and replication.

Among the antiviral strategies make use of anti-oxidants, alpha-tocopherol (**Figure 19**) enjoys a long history since 1960s (263-266). Further researches revealed that alpha-tocopherol (or combination) could normalize the lipid peroxidation processes caused by viral infection (264, 267-272).

The activation of the NADPH oxidase 2 (NOX2) might promote the respiratory symptoms result from infection with influenza A viruses and impede the clearance of the virus (273-277). Therefore, NADPH oxidases became promising novel pharmacologic targets against influenza A virus infection (278-280).

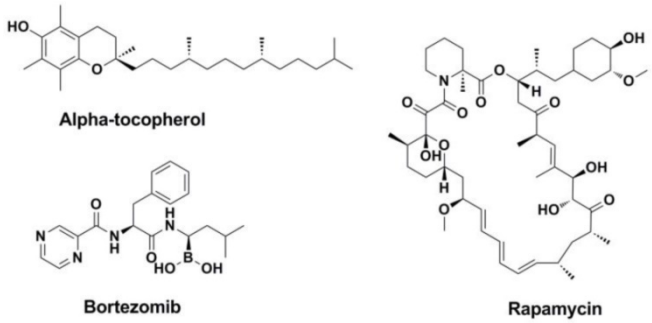

Figure 19. Structures of alpha-tocopherol, Rapamycin and Bortezomib.

3. Other targets and strategies

As described above, the research into the development of anti-influenza drugs has been ongoing for decades and has greatly progressed. However, the drug resistance acquired in recent years from the widespread use of anti-influenza drugs has prompted researchers to find new potential targets.

Pathway inhibitors: The mTOR inhibitor Rapamycin (**Figure 19**), which has been marketed as an immunosuppressive drug that surprisingly leads to the protection from infection with multiple subtypes of the influenza virus (6). In addition, some proteasome inhibitors, such as NFKβ inhibitors (Bortezomib, **Figure 19**), Raf/MEK/ERK pathway inhibitors are also effective and can work as new antivirals against influenza virus (281).

NS1 inhibitors: The non-structural protein 1 (NS1A) of the influenza virus is a small, multifunctional protein that plays a critical role in the response of the host antiviral process (282, 283). When NS1A binds to cleavage and polyadenylation specificity factor (CPSF30), the maturation of the host RNAs is blocked, which leads to the reduction of host proteins (282-286). Twu and co-workers (287) found that the binding of CPSF30 is mediated by the second and third zinc fingers (F2F3) of CPSF30. When the binding process of CPSF30 to the NS1A protein was blocked by a fragment which containing the F2F3 binding motif, the replication of the influenza A virus was inhibited. This work indicated that the CPSF30 binding site in the NS1A protein is a potential target for antiviral therapies against the influenza A virus (287). A recent study carried out by Jablonski *et al.* showed a series of compounds derived from the NSC125044 (**Figure 20,** compound **43**) displayed inhibitory activity against NS1 protein (288).

Phospholipase inhibitors: Phospholipase D (PLD) is one kind of phospholipase that catalyzes the formation of phosphatidic acid, an important messenger in signaling and metabolic pathways (289). Recent studies show that human PLD2 inhibitor such as ML395 (**Figure 20**) possess a broad-spectrum inhibitory against influenza strains (290).

vRNPs inhibitors: As the exportion of influenza virus vRNPs from nuclear has been demonstrated to be mediated by hostexportin 1 (XPO1) (291-293), developing inhibitors of XPO1 to interrupt the vRNP exportion process and then hinder the replicationcycle of the virus make some sense. A study performed by Olivia Perwitasari *et al.* show that verdinexor (**Figure 20**), a novel selective inhibitor of XPO1 selectively and potently inhibited the replication process of various influenza virus A and B strains *in vitro* (294). Resveratrol (**Figure 20**) could interrupt the translocation process of RNPs from the nucleus to the cytoplasm and may be useful as an anti-influenza drug (295-297). Ascorbic and dehydroascorbic acids (**Figure 20**) also possess the antiviral effect, and this effect may work at the envelopment of viral nucleocapsids after the completion of viral DNA replication (298, 299).

RNA inhibitors: RNA inhibitors refer molecule that regulate the expression of gene. RNA inhibitors play important roles in RNA silencing, RNA interference (33) and post-transcriptional regulation of gene expression. RNA inhibitors are able to regulate the expression of influenza viral RNAs. Accordingly, viral genes became a potential target and RNA inhibitors may be effective in influenza treatment (300).

Immunomodulatory agents: Inflammatory changes and other immune reactions that associated with acute coronary syndrome may influence the mortality of influenza (301). Immunomodulatory agents can reduce levels of LDL-cholesterol and improve the inflammatory changes. Studies show that statin treatment in pneumonia patients or influenza patients exhibited reduced mortality (301-304). Other immunomodulatory agents (305) such as

Cyclooxygenase inhibitors (aspirin) (306), ACE inhibitors (ACEIs) (302, 307), angiotensin receptor blockers (ARBs) (302), AMPK agonists (metformin) (308), PPARα and PPARγ agonists (fibrates and glitazones) (309-311), however, showd the ability to reduce mortality in mouse models of influenza (312, 313) and patients with pneumonia (ARBs and ACEIs) (302, 314).

Combination therapies: Combination therapy is one of the prospective domains in the investigation for anti-flu agents. Combination therapies used in anti-influenza treatment may improve the clinical outcomes and enhance antiviral activity against drug-resistant strains. They can also reduce the risk of side effects, dose-related toxicity, mortality and morbidity (315-317). Therefore, combination therapies are recommend in clinical and can be classified in to early combination chemotherapy and sequential multidrug chemotherapy. A classical combination is M2 blockers and NA inhibitors to avoid drug-resistance. Many studies have been carried out to evaluate the efficacy of combination therapies and single-drug treatment, and most combination therapies showed superior outcomes in mice models (272, 318-321).

Conclusion

As drug resistance (often caused by mono-therapy and, sometimes, uncontrolled use in farm animals) (322) and frequent mutations of strains are increasingly serious in the past few years, few drugs can be effective in this situation. The development of antiviral agents is a practical significance topic that has attracted much attention and had made great progress during the past several decades. Small molecular inhibitors are powerful weapon to fight against influenza virus. Small molecular inhibitors function as M2 ion-channel inhibitors, NA inhibitors and protease inhibitors are used in clinical. M2 ion-channel inhibitors were firstly used in clinic but they have shown some defects in clinical use. The quick development of drug-resistance (strains such as H1N1, H3N2 and type B viruses) has limited their clinical use. Alternatively, NA inhibitors are currently the most popular targets of antiviral research (Oseltamivir and Zanamivir are effective against amantadane resistant strains). While arbidol hydrochloride is effective against the influenza A and B viruses, its precise mechanisms of action remain unclear. The usefulness of the marketed NA inhibitors oseltamivir and Zanamivir is also limited due to the increasing prevalence of resistant strains. Besides mono-therapy, combination therapies were also developed (29, 315, 317). Treatment with immunomodulatory agents also represents a new approach to deal with seasonal and pandemic influenza. Along with the determination of the NA structure and the discovery of SAR in recent years, the basis of rational design for novel, potent NAIs is valid. As drug resistance became an increasingly serious problem, and the existing drugs may no longer be useful due to the emergence of mutated strains, researchers have focused on making structural modifications of current drugs to identify potential new targets such as HA (HA) inhibitors, RNA-dependent RNA polymerase (RdRp) inhibitors, nucleocapsid protein (NP) inhibitors, protease inhibitors, V-ATPase inhibitors, Pathway inhibitors, Anti-oxidants, Phospholipase inhibitors, vRNPs inhibitors and RNA inhibitors etc. Some inhibitors of these targets have shown certain anti-influenza activities in vivo and *in vitro*, and further studies are in progress. It is particularly worth mentioning here that major progress was made in unravelling of functioning and mechanisms of the virus polymerase in past few years, as well as novel RdRp inhibitors. It can be anticipated that polymerase inhibitors will reshape the field of influenza prevention and therapy in the near future. There is, however, still a long way to go in winning the battle against influenza pandemics.

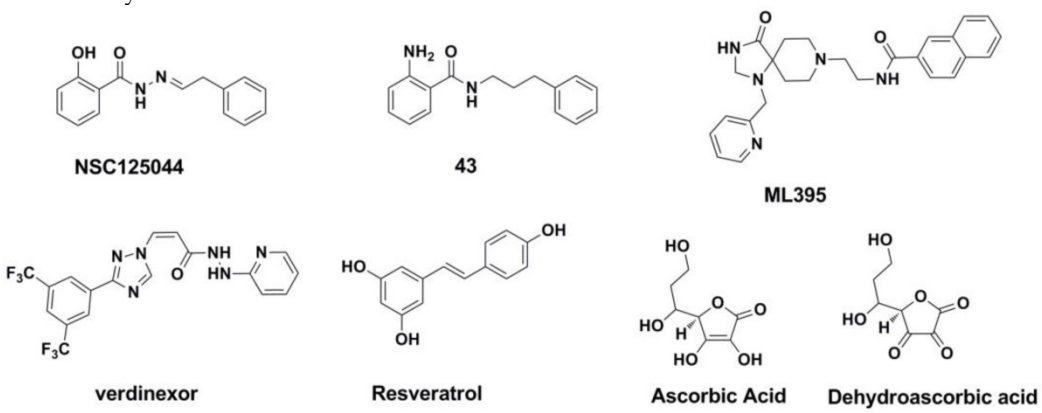

Figure 20. Structures of NS1 inhibitors and phospholipase inhibitors.

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Disclosure

The authors declare no conflict of interest.

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