


# Strategies for developing anti-Hantavirus drugs

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# Strategies for developing anti-Hantavirus drugs

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Hantavirus is a zoonotic enveloped RNA virus belonging to the Bunyavirales order. Hantaviruses are classified into Old and New World clades in systematics. The Old World strains that spread in Eurasia can cause hemorrhagic fever with renal syndrome (HFRS), which is characterized by kidney damage and systemic vascular damage. In contrast, the New World variant unique to the Americas can lead to the rapid development of hantavirus cardiopulmonary syndrome (HCPS), mainly damaging heart and lung tissues. In May 2026, the World Health Organization (WHO) reported an outbreak of hantavirus infection aboard a polar expedition cruise ship that had departed from Argentina in April. The first cases emerged on April 6, with eight confirmed infections subsequently identified. As of May 27, the WHO reported 13 confirmed cases of hantavirus infection, including three fatalities; no additional deaths have been reported since May 2. So far, there is no globally approved antiviral therapy or human prophylactic vaccine for treating Hantavirus infection. Patient management relies entirely on targeted supportive care. This unmet medical need highlights the urgency of developing effective prevention and treatment strategies for Hantavirus disease.

## VIROLOGICAL BASIS FOR ANTI-HANTAVIRUS DRUG DEVELOPMENT

Old World hantaviruses consist of zoonotic pathogens mainly carried by rodents, such as Hantaan virus (HTNV), Seoul virus (SEOV), Puumala virus (PUUV) and Dobrava–Belgrade virus (DOBV). HTNV and SEOV are more widely distributed in Asia. In contrast, New World hantaviruses including Sin Nombre virus (SNV) and Andes virus (ANDV), which are endemic to the Americas, exhibit significantly higher case fatality rates of up to 40%.

The hantavirus genome comprises three segments of single-stranded, negative-sense RNA. These genomic segments are classified by nucleotide length into the small (S), medium (M), and large (L) segments (Figure 1). They encode the nucleocapsid protein (NP), the glycoprotein precursor (GPC), and the RNA-dependent RNA polymerase (RdRp), respectively. The GPC is post-translationally cleaved into two mature envelope glycoproteins, Gn and Gc, which constitute the surface spikes of virions.[1] To date, multiple hantavirus protein structures have been resolved, such as glycoprotein Gc/Gn monomers and tetramers, NP and RdRp. These findings provide a solid structural basis for targeted drug development (Figure 1).

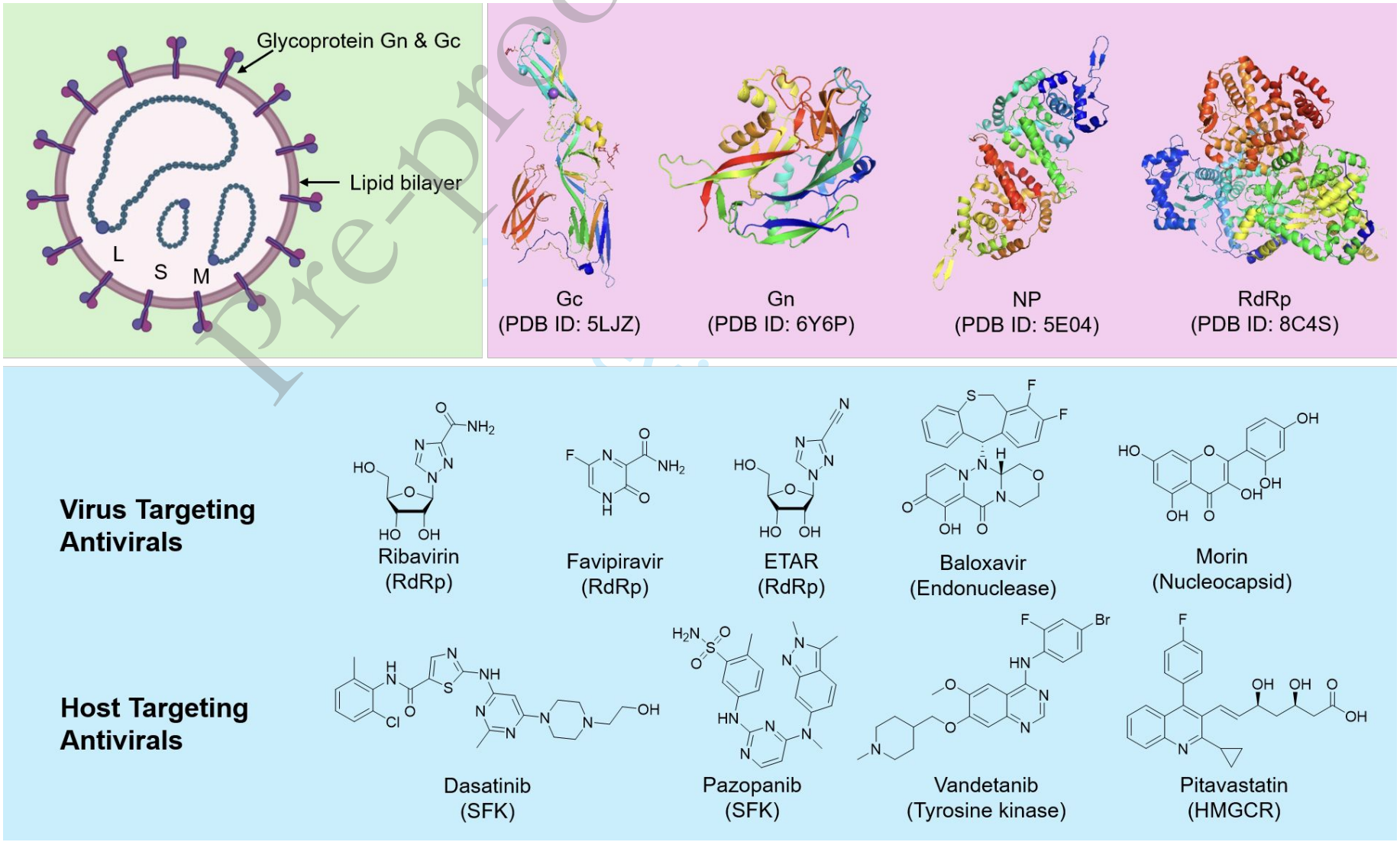
Glycoprotein Gn & Gc
Lipid bilayer
L
S
M
Gc
(PDB ID: 5LJZ)
Gn
(PDB ID: 6Y6P)
NP
(PDB ID: 5E04)
RdRp
(PDB ID: 8C4S)
Virus Targeting Antivirals
Ribavirin
(RdRp)
Favipiravir
(RdRp)
ETAR
(RdRp)
Baloxavir
(Endonuclease)
Morin
(Nucleocapsid)
Host Targeting Antivirals
Dasatinib
(SFK)
Pazopanib
(SFK)
Vandetanib
(Tyrosine kinase)
Pitavastatin
(HMGCR)

Figure 1. Hantavirus structure and crystal structure of a potential drug target, along with corresponding therapeutic agents (Image generated: www.biorender.com and PyMOL).

## KEY LINKS OF VIRAL LIFE CYCLE FOR DRUG TARGETING

Hantaviruses initiate infection by binding their envelope glycoprotein Gn to host cell receptors including integrin. Within the lysosomal compartment, virions undergo uncoating, thereby releasing three viral nucleocapsids into the cytoplasm. Subsequently, the viral RdRp drives transcription through a cap-snatching mechanism to generate three viral mRNAs, one from the S, M, and L sections of the viral RNA. After transcription of viral genes, translation follows. Virion assembly and budding take place at the Golgi apparatus. Then, the viral particle is trafficked to the plasma membrane and subsequently released *via* exocytosis. Pharmacological inhibition of any of these discrete steps effectively suppresses viral replication and intercellular spread.

## VIRUS-TARGETING ANTIVIRAL STRATEGY

Viral entry represents the initial step of infection; therefore, inhibiting this process can effectively prevent viral invasion of host cells. Inhibition of HTNV infection by benidipine hydrochloride was observed in Vero cells, with an $IC_{50}$ of 3.06 μM. By inhibiting membrane-bound calcium channels, calcium channel blockers decrease intracellular calcium concentrations, thereby exerting protective effects on vascular endothelial cells. Moreover, a range of calcium channel inhibitors, including cilnidipine, felodipine, amlodipine, manidipine, nicardipine, and nisoldipine, demonstrate comparable antiviral activity.[2]

RdRp is the central enzyme responsible for hantavirus genome replication and transcription, and represents the most advanced and well-validated target for direct-acting antiviral drug development. Nucleoside analogs constitute the predominant class of RdRp inhibitors; upon incorporation into viral RNA, they induce either premature chain termination or lethal mutagenesis, thereby effectively suppressing viral replication. Ribavirin and favipiravir both inhibited hantavirus infection in a dose-dependent manner. The $IC_{50}$ and $IC_{90}$ values for ribavirin were 2.65 μM and 10.49 μM, respectively, whereas those for favipiravir were 3.89 μM and 9.79 μM, respectively. When administered in combination, the antiviral efficacy of ribavirin is enhanced by the addition of low-dose favipiravir.[3] Structural optimization based on ribavirin yielded 1-$\beta$-$_D$-ribofuranosyl-3-ethynyl-[1,2,4]triazole (ETAR), which exhibited $EC_{50}$ values of 10 μM and 4.4 μM against HTNV and ANDV, respectively.[4] Intraperitoneal administration of ETAR conferred protection to suckling mice challenged with HTNV, yielding approximately 25% survival at doses of 12.5 and 25 mg/kg ETAR, with a median time to death of 17.1 ± 0.7 days.

Baloxavir acid (BXA) targets the endonuclease domain of the PA subunit of viral RdRp, thereby inhibiting the cap-snatching activity of RdRp and ultimately blocking the viral replication cycle. Through an enzyme-linked focus formation assay, BXA exhibited anti-hantavirus activity comparable to that of favipiravir. Based on the high-resolution crystal structure of the ANDV L protein RNA endonuclease domain and computational modeling of the corresponding HTNV

domain, it is plausible that BXA binds to the endonuclease domain of the hantavirus L protein, thereby exerting its inhibitory effect.[5]

Based on the bioinformatics analysis results, the NP of rodent-borne hantaviruses exhibit high amino acid sequence identity, ranging from 59.1% to 97.9%. As the most highly conserved structural protein of hantaviruses, the NP plays pivotal roles in ribonucleoprotein assembly, genomic RNA stabilization, and evasion of host immune responses. Consequently, targeting NP to disrupt its protein–protein and protein–RNA interactions represent a promising and novel antiviral strategy against hantaviruses. The RNA-binding crevice of the hantavirus NP is formed and stabilized by the N- and C-terminal lobes, which predominantly constitute the structural framework of this crevice. Morin inhibits HTNV infection in a concentration-dependent manner ($IC_{50}$ = 8.03 μM), primarily targeting the post-entry viral replication stage. Mechanistic investigations revealed that morin exerts its antiviral activity through direct interaction with the HTNV NP.[6]

## HOST-TARGETING ANTIVIRAL STRATEGY

The expression of cellular adhesion molecules including vascular endothelial (VE)-cadherin and VE growth factor (VEGF) presented dual changes after ANDV infection. ANDV infection also markedly elevated the phosphorylation level of VEGF receptor 2 (VEGFR2). Pharmacological blockade of VEGFR2 kinase activity and inhibition of Src family kinases (SFKs) both remarkably reduced ANDV-triggered endothelial hyperpermeability. In the panel of tested SFK inhibitors, dasatinib and pazopanib exerted prominent effects and blocked over 90% of VE-cadherin dissociation.[7] Vandetanib is a tyrosine kinase inhibitor with selective targeting against VEGFR2. This agent potently inhibited VEGFR2 phosphorylation *in vitro* and further alleviated VE-cadherin degradation.[8]

HTNV elevates cholesterol 25-hydroxylase (CH25H) expression in infected cells. Both CH25H overexpression and exogenous 25-hydroxycholesterol administration markedly inhibit HTNV infection. This inhibition is probably achieved by suppressing 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme of cholesterol biosynthesis. Moreover, cholesterol-lowering drugs (pitavastatin, atorvastatin, simvastatin, and fluvastatin) exert strong anti-HTNV activity.[9]

## IMMUNOTHERAPY

Immunotherapy is an important supplementary strategy for anti-hantavirus treatment, mainly including convalescent plasma therapy and monoclonal antibody (mAbs) therapy. Human convalescent plasma has demonstrated protective efficacy in animal models of infection and lethal

disease, including the ANDV-infected hamster model. In terms of mAbs therapy, multiple highly specific neutralizing monoclonal antibodies targeting hantavirus glycoprotein have been screened and identified. The candidate mAbs JL16 and MIB22 exhibited strong *in vitro* neutralizing activity against ANDV ($IC_{50}$ values were 6.60 and 0.205 μg/mL, respectively).[10] These therapeutics remain subject to several limitations, including epitope profiling of the target antigens and assessment of the therapeutic window for these mAbs. Moreover, challenges associated with producing soluble recombinant ANDV-GP have hindered reliable quantification of mAb binding affinity.

## CURRENT CHALLENGES IN ANTI-HANTAVIRUS DRUG DEVELOPMENT

Substantial advances have been achieved in biological research on hantavirus and the development of antiviral agents. Nevertheless, relevant drug research and clinical translation still encounter multiple challenges. There are significant genetic differences between Old World and New World hantaviruses, leading to great differences in drug sensitivity. For example, Clinical trial results of ribavirin treatment for HFRS caused by PUUV conducted in Russia indicate that intravenous administration of ribavirin did not alter plasma viral load in patients. This may be attributable to its mutagenic effect on the virus without inhibiting viral replication, its therapeutic efficacy being highly dependent on the timing of administration, and the differing correlations between viral load and disease severity in PUUV- versus HTNV-induced HFRS. Most existing candidate drugs only target single viral subtypes, lacking broad-spectrum antiviral activity, which limits their universal clinical application. Developing broad-spectrum anti-hantavirus drugs targeting conserved viral targets is an urgent problem to be solved. In addition, due to the low incidence and sporadic geographic distribution of hantavirus infection, conducting large-scale, multicenter clinical trials is challenging, resulting in a paucity of high-level clinical evidence to substantiate the efficacy and safety of candidate therapeutics.

## FUTURE PERSPECTIVES FOR ANTI-HANTAVIRUS DRUG DEVELOPMENT

Future anti-hantavirus drug development should prioritize both multi-target agents and combinatorial drug regimens to suppress viral replication and regulate host responses simultaneously. These approaches directly act on highly conserved viral proteins including RdRp and NP, alongside host-directed antiviral strategies such as immunomodulation and vascular endothelial protection. Systematic screening of broad-spectrum therapeutic candidates targeting evolutionarily conserved genomic regions across different hantavirus subtypes is essential for developing universal anti-hantavirus treatments. In addition, leveraging artificial intelligence (AI) powered multimodal learning, multi-objective molecular generation, and ultra-rapid virtual screening technologies, this approach enables concurrent multi-target drug design against multiple conserved Hantavirus targets including GPC, NP, and RdRp.

With the advancement of biotechnology, high-throughput drug screening platforms, pseudovirus infection models and human organoid systems will be more widely applied in anti-hantavirus drug discovery. Molecular editing technologies enable precise, targeted modifications of the core scaffolds, cyclic structures, and side chains of candidate molecules to improve their binding compatibility with conserved pockets in the Hantavirus GPC, NP, and RdRp. This technique streamlines the construction of single agents with polypharmacological effects, while tuning physicochemical properties to mitigate off-target toxicity and expand cross-strain antiviral spectrum. These tools can greatly improve screening efficiency and expedite research progress. Meanwhile, the development of standardized animal infection models and unified evaluation criteria for antiviral efficacy will resolve inconsistencies in existing preclinical data, and offer reliable and reproducible technical support for clinical translation. Additionally, targeted multicenter clinical studies may be conducted in endemic regions where hantavirus-induced diseases are highly prevalent.

In conclusion, with the continuous in-depth research on hantavirus pathogenic mechanisms and host-virus interaction, three major drug development strategies including virus-targeted direct antiviral therapy, host-directed therapy, and immunotherapy have been gradually improved, and a number of promising candidate drugs have been screened out. However, the development of anti-hantavirus drugs still faces multiple challenges such as imperfect research models, insufficient broad-spectrum activity, unclear action mechanisms, and lack of clinical evidence. In the future, relying on modern technology (for example, AI), focusing on the development of broad-spectrum dual-target drugs, optimizing drug evaluation systems, exploring combination therapy regimens, and accelerating clinical transformation will be the core directions of anti-hantavirus drug research. The continuous breakthrough of these researches will provide effective therapeutic tools for the prevention and treatment of hantavirus infection and effectively reduce the public health burden caused by hantavirus epidemic.



## FUNDING AND ACKNOWLEDGMENTS

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## AUTHOR CONTRIBUTIONS

S. D. and X. H. wrote and edited the manuscript. J. L. and P. Z. supervised and revised the manuscript. All authors contributed to the manuscript and approved the final version.

## DECLARATION OF INTERESTS

Peng Zhan is an Editorial Board member of The Innovation Drug Discovery and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

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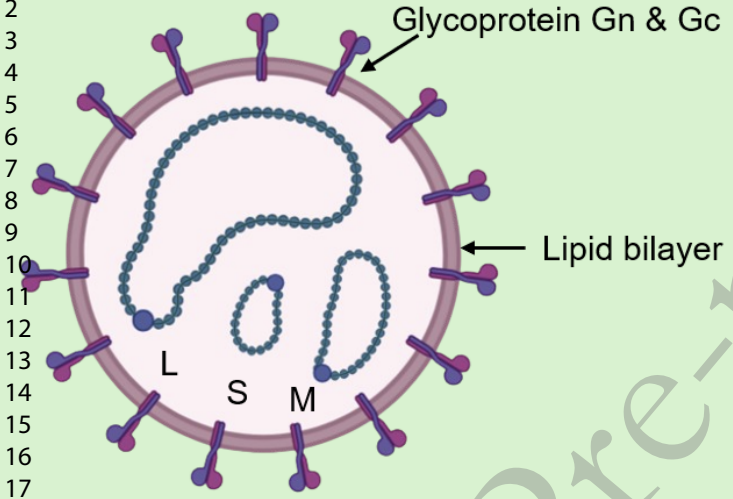
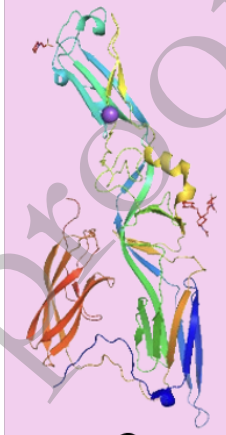
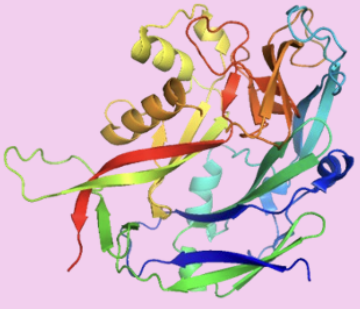
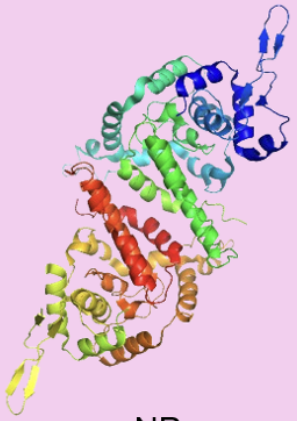


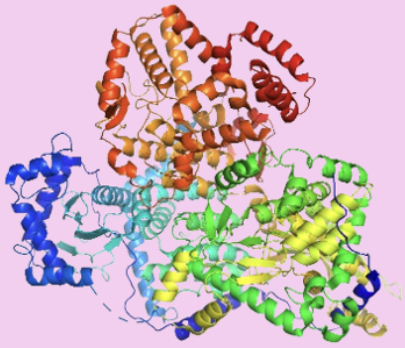
Gc
(PDB ID: 5LJZ)



Gn
(PDB ID: 6Y6P)

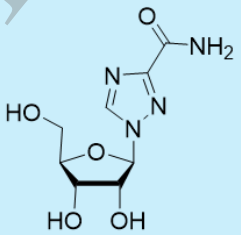


NP
(PDB ID: 5E04)

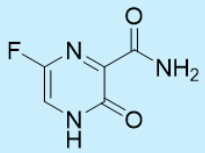


RdRp
(PDB ID: 8C4S)

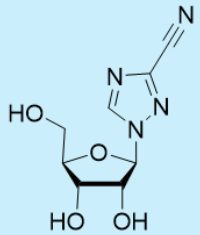
## Virus Targeting Antivirals



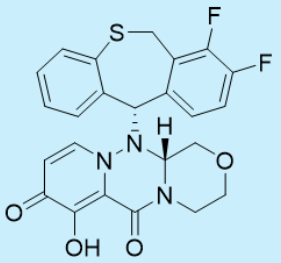
Ribavirin
(RdRp)



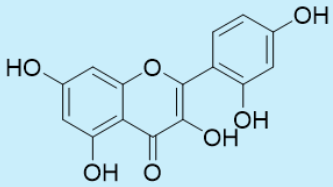
Favipiravir
(RdRp)



ETAR
(RdRp)

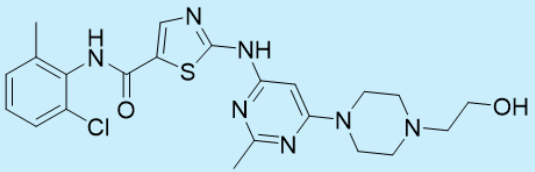


Baloxavir
(Endonuclease)

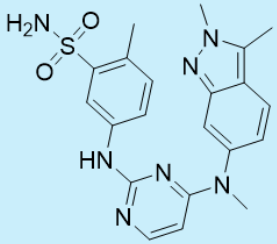


Morin
(Nucleocapsid)

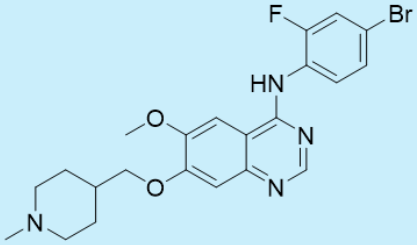
## Host Targeting Antivirals



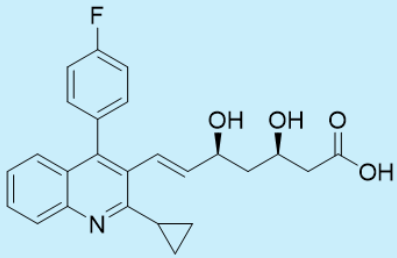
Dasatinib
(SFK)



Pazopanib
(SFK)



Vandetanib
(Tyrosine kinase)



Pitavastatin
(HMGCR)