Master's thesis

NTNU
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Antiviral Drug Combinations for Viral Infection Treatment

Expansion of The AntiViralDualCombi Database and In Vitro Evaluation of Novel Antiviral Drug Combinations Against Echovirus 1

Master's thesis in Pharmacy
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Publication

While writing this thesis, I have had the opportunity to contribute to one publication:

Ianevski, A., Ahmad, S., Anunnitipat, K., Oksenych, V., Zusinaite, E., Tenson, T., Bjørås, M., & Kainov, D. E. (2022). Seven classes of antiviral agents. *Cellular and molecular life sciences : CMLS*, *79*(12), 605. https://doi.org/10.1007/s00018-022-04635-1

Abstract

Enteroviruses, part of the Picornaviridae family, are responsible for a broad range of diseases ranging from asymptomatic to fatal, including rashes, paralysis, meningitis, poliomyelitis, the common cold, hepatitis A, and foot-and-mouth disease. At the time of writing this thesis, no specific treatments for enterovirus infections had been found, highlighting a gap that needs to be addressed.

The AntiViralDualCombi database (AVDC), containing drug combinations, was expanded from an initial 758 to 980 combinations. It was observed that virus-virus target and host-virus target drug combinations predominantly exhibited positive effects, suggesting the potential for novel treatment strategies.

New broad-spectrum antivirals (BSAs) were identified and tested in combination against echovirus-1 in human adenocarcinoma alveolar basal epithelial A549 cells. The drugs utilized in this thesis included vapendavir, vemurafenib, pleconaril, rupintrivir, remdesivir, enviroxime, dipyridamole, sangivamycin, emetine, cycloheximide, anisomycin, and IMP-1088. In total, 65 combinations were tested, and the results revealed that pleconaril combined with anisomycin or cycloheximide exhibited the highest synergy scores. Three combinations showed antagonistic effects: pleconaril or remdesivir plus vapendavir and enviroxime plus vemurafenib. Nevertheless, many other synergistic and additive combinations were also identified.

Combining drugs can be more effective at preventing virus infections than using a single drug and can be done with lower doses. This approach can also reduce side effects when tested in animals and humans, making it a promising strategy for treating EV1 and other enterovirus infections. The identification of these novel combinations, along with the expansion of the AVDC database, provides a solid foundation for further research into effective treatments for enteroviruses. Further testing in preclinical and clinical trials is needed to fully evaluate the potential of these promising drug combinations and contribute to better preparedness and response to future viral outbreaks.

Sammendrag

Enterovirus, som er en del av Picornaviridae-familien, er ansvarlig for et bredt spekter av sykdommer som varierer fra asymptomatiske til dødelige, inkludert utslett, lammelse, hjernehinnebetennelse, poliomyelitt, forkjølelse, hepatitt A og fot-og munnsykdom. På tidspunktet denne avhandlingen ble skrevet, hadde det ikke blitt funnet noen spesifikke behandlinger for enterovirusinfeksjoner, noe som understreker et hull som må fylles.

AntiViralDualCombi-databasen (AVDC) inneholder informasjoner om kombinasjon av legemidler, utvidet fra opprinnelig 758 til 980 kombinasjoner. Det ble observert at virus-virus rettet og host-virus rettet medikamentkombinasjoner viste positive effekter, noe som antyder potensialet for nye behandlingsstrategier.

Nye bredspektrede antivirale midler (BSA-er) ble identifisert og testet i kombinasjon mot echovirus-1 i menneskelige adenokarsinom alveolære basale epitel A549-celler. Legemidlene som ble brukt i denne testen inkluderte vapendavir, vemurafenib, pleconaril, rupintrivir, remdesivir, enviroxime, dipyridamol, sangivamycin, emetin, cycloheximid, anisomycin og IMP-1088. Totalt ble 65 kombinasjoner testet, og resultatene viste at pleconaril kombinert med anisomycin eller cycloheximid hadde de høyeste synergipoengene. Tre kombinasjoner viste antagonistiske effekter: pleconaril eller remdesivir pluss vapendavir og enviroxime pluss vemurafenib. Imidlertid ble det også identifisert en rekke andre synergistiske og additive kombinasjoner.

Å kombinere legemidler kan være mer effektivt for å forhindre virusinfeksjoner enn å bruke et enkelt legemiddel og kan gjøres med lavere doser. Denne tilnærmingen kan også redusere bivirkninger når den testes på dyr og mennesker, noe som gjør det til en lovende strategi for behandling av EV1 og andre enterovirusinfeksjoner. Identifiseringen av disse nye kombinasjonene, sammen med utvidelsen av AVDC-databasen, gir et solid grunnlag for videre forskning på behandlinger for enterovirus. Videre testing i prekliniske og kliniske studier er nødvendig for å fullt ut vurdere potensialet til disse lovende legemiddelkombinasjonene og bidra til bedre beredskap og respons på fremtidige virusutbrudd.

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Abbreviations

A549 cell	Human Adenocarcinoma Alveolar Basal Epithelial Cells
ADE	Adverse Drug Event
AVDC	The AntiViralDualCombi Database
BCC	Broad-Spectrum-Containing Drug Cocktail
BSA	Broad-Spectrum Antiviral
CC50	The Half-Maximal Cytotoxic Concentration
DHODH	Dihydroorotate Dehydrogenase
DMSO	Dimethyl Sulfoxide
EC50	The Half-Maximal Effective Concentration
EV-1	Echovirus 1
EV-71	Enterovirus 71
External ID	External Identifier
FBS	Fetal Bovine Serum
FLUAV	Influenza A Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIV-2	Human Immunodeficiency Virus Type 2
HRV-B14	Rhinovirus 14
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MoA	Mode Of Action
moi	Multiplicity Of Infection
MSA	Most Synergistic Area
NIPH	The Norwegian Institute of Public Health
OSBP	Oxysterol-Binding Protein
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SI	Selectivity Value
SVR	Sustained Virologic Response
TCID50	Median Tissue Culture Infectious Dose

Introduction

Coronaviruses are a family of viruses responsible for multiple outbreaks, including SARS-CoV in 2002, MERS-CoV in 2012, and the current COVID-19 pandemic caused by SARS-CoV-2[1]. The COVID-19 pandemic has had a more significant impact than previous outbreaks, infecting over 36 million people and causing over a million deaths worldwide. At the pandemic's onset, no specific treatments or vaccines were available, highlighting the urgent need for prevention strategies to mitigate both human and economic consequences, such as healthcare costs, lost productivity, and social disruption [2].

A new medication can generally take 10–15 years to develop. Typically, multiple stages are involved in the year-long drug development process, including the discovery, preclinical, and clinical phases 1–3, and approval and post-approval phases. The extended procedures are essential to ensure that the drugs produced are secure and effective regardless of the patient's age or race [3]. The cost of developing a new drug has risen in recent years [3]. When the costs of unsuccessful drugs that have not reached the market are considered, the estimated cost to develop a new drug that has reached the market is over $1.5 billion. Additionally, according to a study on attrition rates, only 11% of drugs for all therapeutic areas are successfully developed, which points to a high attrition rate in drug development [4]. The high attrition rate in drug development has been linked to several probable factors, including inadequate clinical efficacy, uncontrollable toxicity, undesirable drug-like characteristics, insufficient commercial demands, and faulty planning [5]. In conclusion, it can be challenging for pharmaceutical companies and humanity when a severe pandemic occurs unexpectedly.

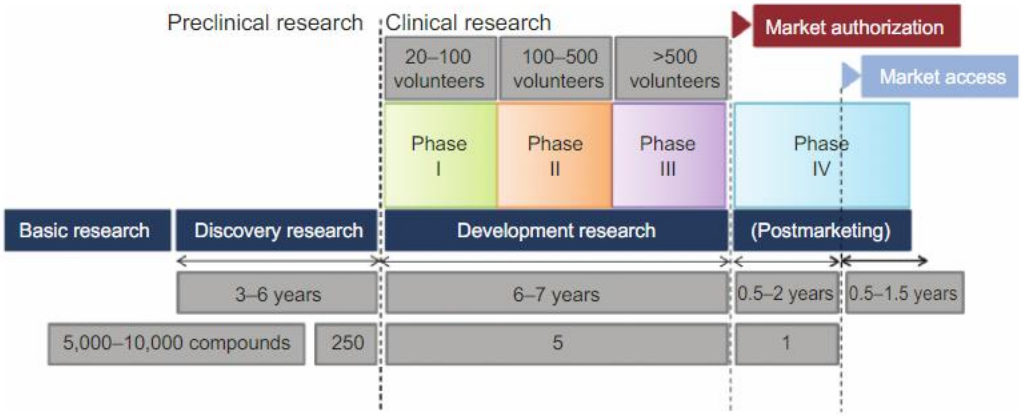


Figure 1. shows the process of developing new drugs. It starts with basic research and ends with post-marketing surveillance. Drug companies follow a simplified sequence of steps to create new drugs, including selecting the disease to target and identifying lead compounds through various methods. Once identified, compounds undergo tests to assess their safety, pharmacokinetics, and pharmacodynamics. Clinical trials are then conducted in Phase I and II to test the drug's safety and efficacy in healthy volunteers and the target population. Phase III confirms the clinical doses, frequency, and timing of administration for approval. Post-marketing trials in Phase IV monitor the drug's safety and detect harmful effects. The drug can be withdrawn from the market if toxic effects are discovered during this phase [3].

Developing new drugs is a challenging and costly process that often fails. To address this, some recommend drug repurposing, also known as drug repositioning, as a possible alternative [6]. Skipping preclinical trials for certain drugs can allow them to move directly to phase II clinical trials once safety assessments and formulation development have been completed, resulting in lower costs and faster development times [7]. The goal is to identify new uses for approved or investigational drugs, making drug repurposing a potential option for treating the infection. By utilizing drugs that have already undergone clinical trials and have established safety and pharmacological profiles, drug repurposing can significantly reduce development costs and accelerate the drug development process [7]. In the case of COVID-19, supportive treatments such as oxygenation, ventilation, and fluid management were the primary treatments [8]. Hydroxychloroquine, an antimalarial drug commonly used for rheumatoid arthritis and lupus erythematosus [9], was initially proposed and used to combat viral infections during the pandemic's emergence [8][10]. However, subsequent studies yielded inconclusive results or

showed no clinical benefit, leading to hydroxychloroquine no longer being recommended for treating COVID-19 patients [10][11].

Another challenging aspect of developing antiviral drugs is that viruses can quickly develop resistance to them. The risk of resistance is influenced by factors such as how well the virus can replicate, how fast the drug can stop replication, and the number of genetic mutations required for the virus to resist the drug [12]. Drugs that can quickly hinder viral replication have a lower risk of resistance. Additionally, the genetic barrier is an essential factor and refers to the number of mutations a virus must accumulate to replicate efficiently in the presence of an antiviral agent [12]. To reduce the risk of drug resistance, combining broad-spectrum antivirals (BSAs) can be helpful. It can increase their effectiveness while minimizing the chances of developing drug resistance [13]. Alternatively, antivirals that target protein-protein interactions could be developed instead of the active sites of viral or host enzymes [14].

The combination of two or more drugs that produce an effect greater than expected is called a synergistic or superadditive effect. Conversely, when two or more drugs are combined, and the result equals the sum of their individual potencies, it is considered an additive effect [15]. Synergistic and additive effects are often desired in combination therapies, while antagonism refers to a combined effect that is less than expected [15][16]. Combination therapy is widely used to treat various diseases, including cancer, infections, and pain management [15]. Similarly, antiviral drug combinations, or broad-spectrum-containing drug cocktails (BCCs), are also used in virus infection therapies. BCCs are now widely used for treating various diseases, including HIV and HCV [14]. These combinations typically involve two or more antiviral drugs, such as abacavir/dolutegravir/lamivudine for HIV and ledipasvir/sofosbuvir and sofosbuvir/velpatasvir for HCV [14]. BCCs have been shown to reduce the required concentration of antiviral drugs, lowering their toxicity and side effects, and decreasing the development of resistance [13].

Combining different drugs to treat a disease, including viral infections, may have drawbacks. It can lead to more side effects and drug interactions since the occurrence of adverse drug events (ADE) positively correlates with the number of medications used, especially in older adults who

often use more medication [17]. This will lead to potential drug-drug interactions. Additionally, some people may find it difficult to take a lot of pills.

In addition to SARS-CoV-2, which has demonstrated the significant impact a virus outbreak can have on everyone, echovirus 1 (EV-1) is another important virus that requires attention due to the absence of approved antiviral drugs for treatment [22]. Consequently, EV-1 will be the focus of this thesis. EV-1 is a member of the enterovirus B group and is a part of the Picornaviridae family, which consists of positive-sense single-stranded RNA viruses found in humans and animals worldwide [18][19]. The Picornaviridae family is a large family of vertebrate viruses [20], consisting of 63 genera containing 147 species [21], including several important human picornaviruses such as poliovirus, rhinovirus, and hepatitis A virus, which transmit via fecal-oral or respiratory routes. These viruses have historically played a significant role in human and animal health [20]. They are responsible for a wide range of asymptomatic to fatal diseases, including rashes, paralysis, meningitis, poliomyelitis, the common cold, hepatitis A, and foot-and-mouth disease [18][19]. Moreover, there is increasing interest in enterovirus research due to evidence linking these viruses with type I diabetes, asthma, and myocarditis [18]. Besides the enterovirus B group, the genus has 11 species: enteroviruses A, C-H, and J and rhinoviruses A-C [22]. Only enteroviruses A, B, C, and D, as well as rhinoviruses A to C, can infect humans [20].

Enterovirus species	Types
Human enterovirus A	Human Coxsackievirus A2–8, 10, 12, 14, 16. Human enterovirus 71, 76, 89–92.
Human enterovirus B	Human Coxsackievirus A9, B1–6. Human echovirus 1–9, 11–21, 24–27, 29–33. Human enterovirus 69, 73–75, 77–88, 93, 97, 98, 101, 106, 107.
Human enterovirus C	Human poliovirus 1–3. Human Coxsackievirus A1, 11, 13, 15, 17–22, 24. Human enterovirus 95, 96, 99, 102, 104, 105, 109.
Human enterovirus D	Human enterovirus 68, 70, 94.
Human rhinovirus A, B, C *Porcine enterovirus B* *Bovine enterovirus* *Simian enterovirus A*	

Figure 2 shows various species and examples of their serotypes. Echovirus 1 is a serotype belonging to the human enterovirus B species [23].

Treating enterovirus infections is challenging as no approved antiviral drugs are available. Clinical trials of a capsid-binding agent, pleconaril, and a 3C protease inhibitor, rupintrivir, showed limited efficacy or side effects. However, recent research has made progress in developing new anti-enteroviral drugs with both in vitro and in vivo antiviral efficacy. One in vitro study has identified promising synergistic drug combinations such as rupintrivir–vemurafenib, vemurafenib–pleconaril, rupintrivir–pleconaril, and rupintrivir–cycloheximide against enterovirus EV-1 infection [22]. Despite showing promising synergistic effects against EV1, further clinical studies are required to determine their efficacy and safety.

Improving our ability to treat virus infections relies on predicting and expanding new antiviral drug combinations. Therefore, this is essential to have a comprehensive and reliable database. In 2022, my research group launched the updated version of their previous DrugVirus.info database, DrugVirus.info 2.0[24]. This database now contains information on 255s BSAs and 407 BCCs,

along with added analysis functions. By utilizing the most current data, researchers can gain valuable insights into BSAs and BCCs, which will help to improve our understanding of drugs and drug combinations. Ultimately, this will aid in responding to new virus outbreaks and developing effective treatments more efficiently. This database will also be beneficial in combating future unpredictable outbreaks, hoping to reduce mortality.

Aim and Objectives

During the COVID-19 pandemic, it became clear that rapid actions were crucial to minimize the financial and health-related problems caused by the virus outbreak. This lesson is also significant for handling future unexpected disease outbreaks promptly.
A past master's student developed a valuable database called AntiViralDualCombi (AVDC), which focuses on two-drug combinations used to treat various viral infections. Within this database are 533 distinct two-drug combinations, 337 different antiviral drugs, and information on 52 unique viruses. Some new drug combinations were discovered and added to the database found at Drugvirus.info [25]

The primary focus of this project is on two key objectives. The first objective is to broaden the scope of the AVDC database, which will also serve to update the existing Drugvirus.info 2.0 database. The goal is to make the database more comprehensive by collecting additional scientific and clinical data on antiviral drug combinations. Furthermore, this project will gather information on the effects of these combinations within the AVDC database, which has yet to be undertaken. The enhanced database will prove beneficial for researchers requiring quick access to information about these drug combinations.

The project's second objective is to identify novel drug combinations that demonstrate an effective effect against echovirus-1 in cell culture, thus providing proof of concept. The specific combinations will be based on the outcomes of the mono-drug experiment carried out by my research team. Promising drugs that exhibit effects on EV-1 will be evaluated in combination, supplemented by some drugs from previous research. The choice to concentrate on echovirus-1 comes from biosafety level restrictions and the project's timeframe. Additionally, this virus is consistent with my team's research interests, as demonstrated by a 2022 article discussing an anti-enteroviral drug combination [23]. By accomplishing these objectives, the project intends to support ongoing efforts against viral diseases, enhance preparedness for future outbreaks, and reveal some innovative BCCs that could be further investigated.

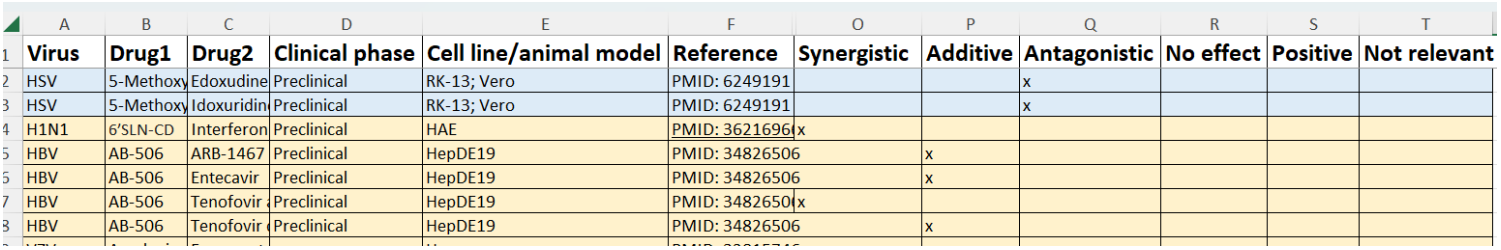
Material and Methods

The methods for this project will be split into two parts. The first part involves expanding the AVDC data and updating the Drugvirus.info database, using Microsoft Excel 365 to record the information. This section will explain the strategies and Excel formulas used for expansion and updating. The process will be adapted from the approach used by a previous master's student while ensuring clarity and consistency.
The second part focuses on the drug combination experiment. This section will describe how we chose the drugs for the experiment and explain how the experiments were carried out.

3.1 Expanding the AVDC database and Updating DrugVirus.info

3.1.1 Finding New Combinations for the AVDC Database

The AVDC database, created by a previous master's student, is recorded in an Excel file with 758 combinations, containing 533 unique antiviral drug combinations, 52 distinct viruses, and 338 individual antiviral drugs [25]. To expand the database, search terms such as "antiviral combinations," "synergistic and antiviral combination", and "antagonism and antiviral combination" were used in PubMed. The search was restricted to articles published after January 2022, and only publications in English or with English abstracts were manually reviewed. Information regarding the first and second drugs, viruses, cell lines, and references was collected in the Excel file. The effects of the combinations were categorized as "synergistic," "additive," "antagonistic," "no effect," "positive," or "not relevant," as described in section 3.1.5 and recorded accordingly.
Each drug combination was searched on ClinicalTrials.gov to determine if it had advanced further in clinical trials or been tested in human clinical studies. If combinations were not already in the database or had advanced in the clinical phase and met the specified criteria, they were recorded.



	A	B	C	D	E	F	O	P	Q	R	S	T
1	Virus	Drug1	Drug2	Clinical phase	Cell line/animal model	Reference	Synergistic	Additive	Antagonistic	No effect	Positive	Not relevant
2	HSV	5-Methoxy	Edoxudine	Preclinical	RK-13; Vero	PMID: 6249191			x			
3	HSV	5-Methoxy	Idoxuridin	Preclinical	RK-13; Vero	PMID: 6249191			x			
4	H1N1	6'SLN-CD	Interferon	Preclinical	HAE	PMID: 3621696	x					
5	HBV	AB-506	ARB-1467	Preclinical	HepDE19	PMID: 34826506		x				
6	HBV	AB-506	Entecavir	Preclinical	HepDE19	PMID: 34826506		x				
7	HBV	AB-506	Tenofovir	Preclinical	HepDE19	PMID: 3482650	x					
8	HBV	AB-506	Tenofovir	Preclinical	HepDE19	PMID: 34826506		x				

Figure 3 shows a screenshot of drug combinations and variable data corresponding to the antiviral cocktails.

3.1.2 Standardization of Drug Nomenclature for the AVDC Database

In the AVDC database, some articles used generic names or external identifiers (external IDs) as drug names, which could lead to duplicated data. DrugBank Online, an online database containing information about drugs and drug targets, was used to standardize drug names. All collected drug names were manually searched on DrugBank to find the actual drug names. For drugs without records on DrugBank, a Google search was conducted.

Virus abbreviations were also standardized using an internal database that provides Virus IDs (virus abbreviations), virus names, and other relevant information about the viruses. The virus abbreviations were checked for consistency with the internal database by using the Xlookup function in Excel to compare Virus IDs in the AVDC and internal virus databases. Virus IDs not found in the internal database returned an error.

3.1.3 Standardization of Drug Ordering

Once all drug names were standardized, they were sorted vertically and horizontally in alphabetical order to avoid confusion and duplication of data with the same combinations recorded as Drug 1-Drug 2 and Drug 2-Drug 1. The drug order was arranged horizontally using the IF function in Excel, and details on the formula and explanation will be provided later. The drug combinations were sorted vertically using the "Sort A to Z" option in the tool menu. The accuracy

of the updated drug orders was then manually reviewed.

	A	B	C	R	S	T
1		Before rearranging		After rearranging		
2	Virus	Drug1	Drug2	Drug1	Drug2	Clinica
3	PV	Disoxaril	Arildone	Arildone	Disoxaril	Preclinical
4	PV	Disoxaril	Ethyl 4-Methyl-2-(M	Disoxaril	Ethyl 4-Methyl-2-(Methylthi	Preclinical
5	PV	Disoxaril	Guanidine	Disoxaril	Guanidine	Preclinical
6	FLUAV	Peramivir	Ribavirin	Peramivir	Ribavirin	preclinical
7	HSV-1	Aphidicolin	Acyclovir	Acyclovir	Aphidicolin	Preclinical

Figure 4 illustrates the change in the order of drug combinations before and after they were rearranged using IF function. The cells highlighted in yellow show the combinations that were rearranged.

3.1.4 Data Recording Methods for the AVDC Database

It is important to record each unique drug combination only once to avoid data duplication and potential impacts on analysis outcomes. If the same combination of drugs was tested in the same cell line against the same virus, it was considered identical and not re-recorded. However, drug combinations tested against different cell lines or viruses, even if using the same individual drugs, were recorded because they can provide different outcomes.

For drug combinations that progressed through clinical stages, such as from clinical phase 2 to phase 3, only the combination at the most advanced clinical phase was recorded. The database focuses on human BSA combinations, so studies on viruses in animals were not included.

3.1.5 Removal of Duplicate and Less Clinically Advanced Combinations from the AVDC Database

After alphabetically rearranging the list, duplicate combinations were removed using the Remove Duplicates function in the toolbar. The process began by assigning a unique number to each combination, starting from 1 and continuing to the last combination. A copy of the datasheet was made to track the removed data and to compare which combinations were eliminated. The columns for "Drug 1", "Drug 2", "Clinical Phase", and "Cell Line/Animal Model" were selected, and the

Remove Duplicates function was applied. Following this, unique combinations based on these four variables remained. The Xlookup function was used to compare the two datasheets (the unique number) and identify any missing combinations. Any removed combinations were manually rechecked with their corresponding combinations for accuracy.

3.1.6 Categorization of Combination Effects in the AVDC Database

Antiviral combinations have been studied in both preclinical and clinical research. The classification of these studies as synergistic, additive, or antagonistic is often determined during the preclinical phase. Effects of combinations were recorded based on how the results were presented in the articles. Many studies tested the same combinations at different concentrations, yielding various outcomes, and the presented results were recorded. If combinations had no positive or negative impact or produced statistically insignificant results, they were considered to have no effect.

Studies were classified as positive if they reported a favorable outcome without specifying whether the effects were synergistic or additive. Positive results in human clinical studies included high sustained virologic response (SVR), protective effects, or conclusive positive outcomes. Preclinical studies were considered positive if they demonstrated a decrease in the half-maximal effective concentration (EC50) when two drugs were used together or if favorable results were observed without explaining the nature of the effect.

Studies without a full text or whose impact could not be determined from the abstract were considered irrelevant. Articles in languages other than English or Norwegian or without access to the original article were also deemed irrelevant. Studies that presented results where the effect could not be established were also considered irrelevant.

3.1.7 Combining the AVDC Database with Drugvirus.info

In this expanded AVDC database, BCCs were found by comparing it with the DrugVirus.info database, which lists 255 drugs targeting or used for different viruses. By using the Xlookup function to fill in information for all drugs in Drug 1 and Drug 2 columns, it was possible to identify which drugs are classified as BSAs to date. Afterwards, the filter function was applied to display only combinations containing at least one BSA. This process allowed for the identification of BCCs in the database.

3.1.8 Adding BCCs to The DrugVirus.info Database

After the BCCs in the AVDC database were identified, they were incorporated with the BCCs in the DrugVirus.info Database. There were some discrepancies in drug and virus naming. However, these issues were addressed by standardizing drug and virus nomenclature (as outlined in section 3.1.2) and organizing drug orders (as explained in section 3.1.3). Removing duplicate data was also performed, as described in section 3.1.5. It resulted in a database containing only BCCs, which will be used to update the DrugVirus.info database.

Table 1 presents the formulas along with a brief explanation of their functions.

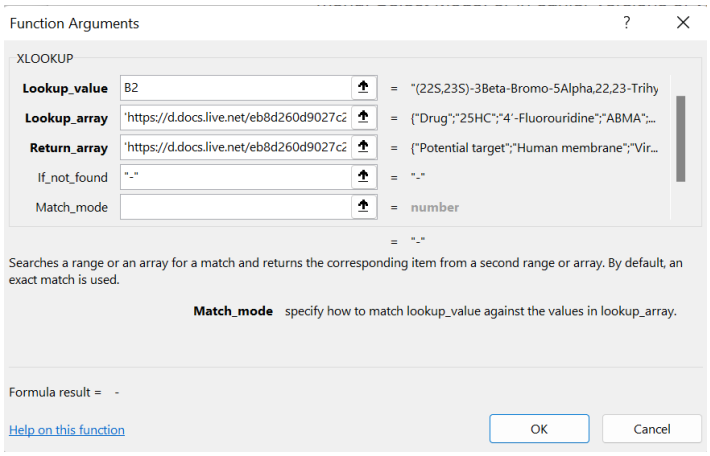
Formula	*Explanation*
IF function *Examples* *=IF (A1<B1, A1, B1)* *Or* *= IF(A1>B1, A1, B1)*	"IF (A1<B1, A1, B1)" is used to compare values in cells A1 and B1, representing Drug 1 and Drug 2 names, which allows for horizontal sorting of data containing both alphabetic characters and numbers. If the value in cell A1 is less than the value in cell B1, the formula returns the value in cell A1, which should be placed in the Drug 1 column. Contrarily, if the value in cell B1 is greater than or equal to the value in cell A1, the formula returns the value in cell B1. On the other hand, "IF(A1>B1, A1, B1)" has a similar function. If the value in cell A1 is greater than the value in cell B1, the formula returns the value in cell A1, which should be placed in the Drug 2 column.
Xlookup function 	"XLOOKUP" has been utilized to standardize drug nomenclature, remove duplicates, and merge the AVDC database with DrugVirus.info. This function allows searching within a range or an array for a specific value and returning a corresponding value in the same position from another range or array

Figure 5 shows the window tool of the Xlookup function in Microsoft Excel.	

3.2 Experiment

3.2.1 Drugs

Compounds were prepared as 10 mM stock solutions by dissolving them into dimethyl sulfoxide (DMSO; Sigma-Aldrich, Hamburg, Germany). These solutions were stored at -80 °C until use. The compounds used in the experiments, along with their suppliers, can be found in the Appendix section.

3.2.2 Cell Cultures

A549 human adenocarcinoma alveolar basal epithelial cells were cultivated in Dulbecco's Modified Eagle Medium (DMEM; Gibco, Paisley, Scotland) enriched with 10% FBS and a blend of 100 U/mL penicillin and 100 µg/ml streptomycin. The cell cultures were maintained at 37°C with 5% CO.

3.2.3 Virus

Echovirus 1 (Farouk strain; ATCC) was supplied by Prof. Marjomäki from the University of Jyväskylä. It was amplified in a monolayer of the A549 cell line using DMEM media containing 0.2% BSA and Pen-Strep. All virus stocks were stored at -80°C.

3.2.4 Drug Test

Cells were seeded at approximately 4×10^4 cells per well in 96-well plates. After 24 hours of growth in DMEM medium supplemented with 10% FBS and a mixture of 100 U/mL penicillin and 100 μg/ml streptomycin, the medium was replaced with DMEM medium containing 0.2% bovine serum albumin and a mixture of 100 U/mL penicillin and 100 μg/ml streptomycin. The compounds were added to the cells in 3-fold dilutions at seven different concentrations starting from 30 μM. Subsequently, cells were infected with viruses at a multiplicity of infections (moi) of 0.1. After 48 hours of infection, the medium was removed from the cells and a Cell Titer Glow assay was used to measure the viability of mock- and virus-infected cells.

3.2.5 Virus Quantification

Virus production is assessed in both compound-treated and untreated cells. The media from the cells were serially diluted (10-fold) from 10^{-2} to 10^{-7} in serum-free growth media containing 0.2% bovine serum albumin. These diluted samples were then applied to a monolayer of A549 cell plates. After 1 hour, cells were overlaid with a virus growth medium containing 1% carboxymethyl cellulose and incubated for 48 hours. The plaques in each well were counted and expressed as plaque-forming units per mL (pfu/mL).

3.2.6 Drug Combination Test and Synergy Calculation

Cells were treated with increasing concentrations of drug combinations. These drug combinations were applied to A549 cell cultures, which were then infected with either EV1 or a mock virus. After 48 hours, the viability of the infected cells was assessed using the CellTiter-Glo assay. The observed responses were compared with the expected combination responses to determine if the drug combination exhibited synergistic effects. The expected response on the viability of virus- and mock-infected cells was established using the Bliss reference model via SynergyFinder. In the Bliss independence model, it is assumed that two drugs exert their effects independently through a stochastic process, allowing the expected combination effect to be calculated based on the probability associated with independent events.

Result

4.1 AVDC database

4.1.1 Expanding the AVDC Database

The initial AVDC database comprised 758 combinations, including 533 unique drug combinations, 52 distinct viruses, and 337 drugs. 261 drug combinations were identified and added to the AVDC database during this expansion. All AVCs in the AVDC database were reviewed. Articles with secondary data, such as reviews, meta-analyses, and duplicates, were removed from the database to avoid data inflation. Combinations that advanced in clinical phases were also removed.

The updated database ultimately contains 980 AVCs, with 39 combinations removed. This expanded AVDC database features 61 unique viruses, 405 different drugs, and 701 distinct drug combinations. SARS-CoV-2 is the most prevalent virus in the database, found in 136 combinations, accounting for almost 14% of the total 980 combinations. It is followed by HCV and FLUAV, representing 9.90% and 9.39%, respectively. A considerable number of articles on HIV do not specify whether they tested drug combinations on HIV-1, HIV-2, or both; thus, data for HIV are collected in two separate categories. Furthermore, 15 viruses represent 80% of the viruses in the database.

Table 2 displays the top 15 most common viruses in the expanded AVDC database, accounting for 80 % of the 980 drug combinations. The amounts are presented both numerically and as percentages.

Virus	*Amount presented*	*Amount %*	*Cumulative %*
SARS-CoV-2	136	13,88 %	13,88 %
HCV	97	9,90 %	23,78 %
FLUAV	92	9,39 %	33,16 %
HIV-1	67	6,84 %	40,00 %
HBV	66	6,73 %	46,73 %
CMV	63	6,43 %	53,16 %
HSV-1	62	6,33 %	59,49 %
EBOV	50	5,10 %	64,59 %
HSV-2	41	4,18 %	68,78 %

HIV	27	2,76 %	71,53 %
PV-1	25	2,55 %	74,08 %
ECHOV-1	19	1,94 %	76,02 %
VZV	18	1,84 %	77,86 %
CHIKV	18	1,84 %	79,69 %
EV-A71	15	1,53 %	81,22 %

The database shows that ribavirin is the most common drug, appearing in 119 combinations, constituting 6% of all available data. Interferon-alpha and antibodies rank second and third, representing 6.64% and 3.83% of the total. It should be noted that a combination may include two antibodies. Out of the 980 combinations, the preclinical phase is the most prominent, with 769 combinations, while 159 combinations are in the clinical phase.

In the AVDC database, 205 combinations were identified as BCCs, signifying that at least one drug in the combination is classified as a BSA according to the existing BSA database. Of these, 61 combinations were found using the existing articles in the AVDC database, while 144 combinations were identified through searches. Remdesivir is the most prevalent drug, appearing in 32 combinations, followed by ribavirin in 19 combinations.

Table 3 displays 33 drugs, accounting for 50% of the 405 different drugs in the expanded AVDC. Cell occupancy is used rather than the number of drugs present in combinations, as some combinations may include the same drug.

Drug	*Cell occupied*	*Cell Occupied %*	*Cumulative %*
Ribavirin	119	6,07 %	6,07 %
Interferon Alpha	91	4,64 %	10,71 %
Antibodies	75	3,83 %	14,54 %
Acyclovir	56	2,86 %	17,40 %
Oseltamivir	50	2,55 %	19,95 %
Favipiravir	43	2,19 %	22,14 %
Remdesivir	36	1,84 %	23,98 %
Foscarnet	35	1,79 %	25,77 %
Tenofovir	32	1,63 %	27,40 %
Zidovudine	32	1,63 %	29,03 %
Sofosbuvir	32	1,63 %	30,66 %
Interferon Beta	32	1,63 %	32,30 %
Ganciclovir	31	1,58 %	33,88 %
Rupintrivir	25	1,28 %	35,15 %
Cidofovir	25	1,28 %	36,43 %
Lamivudine	25	1,28 %	37,70 %
Interferon Gamma	22	1,12 %	38,83 %
Vidarabine	21	1,07 %	39,90 %
Ritonavir	21	1,07 %	40,97 %
Daclatasvir	19	0,97 %	41,94 %
Molnupiravir	16	0,82 %	42,76 %
Maribavir	15	0,77 %	43,52 %
Enviroxime	14	0,71 %	44,23 %
Nitazoxanide	13	0,66 %	44,90 %
Entecavir	13	0,66 %	45,56 %
Adefovir	13	0,66 %	46,22 %
Mycophenolic Acid	12	0,61 %	46,84 %
Peramivir	11	0,56 %	47,40 %
Lopinavir	11	0,56 %	47,96 %
Brivudine	11	0,56 %	48,52 %
Alisporivir	11	0,56 %	49,08 %
Artesunate	11	0,56 %	49,64 %
Selenazofurin	11	0,56 %	50,20 %

4.1.2 Drug Properties and Effects in the AVDC Database

In this expansion, the effects of the combinations were also recorded to explore the relationship between drug combinations and their impacts. Despite having only 980 combinations, 1055 effects were recorded since different concentrations of drugs in a combination can result in varied outcomes. The data revealed that 442 drug combinations exhibited synergistic effects, 170 demonstrated additive effects, and 198 displayed positive effects. Furthermore, 66 combinations showed antagonistic effects, while 27 had no effect. A total of 152 combinations were recorded as not relevant due to the lack of access to full-text articles or inconclusive data, which limited the understanding of other interactions within the combinations.

By integrating with the DrugVirus.info database about BSAs, information on drug targets and modes of action was obtained, allowing for further analysis. A total of 770 combinations were found to exhibit synergistic, additive, positive effects, or a combination of these effects. Even if some of these combinations also displayed antagonistic effects at specific concentration ranges, any combination with positive effects was also included.

For 180 combinations, neither Drug 1 nor Drug 2 had recorded information about drug targets. In 355 combinations, only one drug had a defined target. In 27 combinations, both Drug 1 and Drug 2 targeted human cell components, while 70 combinations had either Drug 1 or Drug 2 acting against viral cell components. Among the combinations, 129 had both Drug 1 and Drug 2 targeting viral components, such as viral DNA or RNA. Additionally, 6 combinations included a drug that targeted both human and viral components.

Table 4 presents the simplified distribution of target components, indicating whether the drugs target the virus, the human host, or both, based on the information acquired through integration with DrugVirus.info. The term "N/A" is used when no information regarding a drug's target is available in the DrugVirus database.

	Drug 2 Target				
Drug 1 Target	**Human**	**Human; Virus**	**Virus**	**N/A**	**Total**
Human	27		32	25	84
Human; Virus			3	3	6
Virus	38	6	129	185	358
N/A	25	3	114	180	322
Total	90	9	278	393	770

Focusing on combinations in which both drugs target viral components, it is observed that the most common combinations in our database involve both drugs targeting viral RNA, represented in 16 combinations. This is followed by combinations where both drugs target viral DNA or one drug targets both viral RNA and DNA, as shown in Table 5.

Table 5 presents a subset of the drug combinations targeting virus-virus interactions.

	Unknown; Viral ion channel	Unknown; Viral neuraminidase	Unknown; Viral protease	Unknown;Viral neuraminidase	Unknown;Viral protease	Viral DNA pol	Viral DNA pol; Viral RNA pol	Viral DNA pol; Viral RNA pol; Viral RT	Viral DNA pol; Viral RT	Viral DNA pol;Viral RNA pol	Viral DNA pol;Viral RNA pol;Viral RT	Viral DNA pol;Viral RT	Viral glycoprotein	Viral NS5A	Viral protease	Viral RNA pol	Viral RNA pol; Viral RT	Viral RNA pol;Viral RT	Viral RT	Viral VP1
Unknown; Viral ion channel																				
Unknown; Viral protease									1											
Unknown;Viral neuraminidase	1	1														3				
Unknown;Viral protease			1													1				
known;Viral RT											1									
al DNA pol						7	7	2		3	7		4			1				
Viral DNA pol;Viral RNA pol						2		1			2	1							1	
Viral DNA pol;Viral RNA pol;Viral RT							2	2			1	6				2				
al DNA pol;Viral								2	1		2									
al glycoprotein						1	1				1					1				
al NS5A											1				1	6				
al protease			2											1		2		1		
Viral protease;Human protease	1															4				
al RNA pol	2	1		1				1			1				4	16			1	
al RNA pol;Viral RT								1												
al RT				2		2		1			5	1				3			3	
al VP1															1					

Focusing on the combinations in the AVDC database that provide positive effects against viruses in the Picornaviridae family, it is observed that most drug targets are not present in our BSA database. Common drug combinations primarily target either viral components or, in some cases, human components such as human oxysterol-binding protein (OSBP) or human dihydroorotate dehydrogenase (DHODH).

Table 6 presents the drug combinations that exhibit synergistic, additive, or positive effects against the Picornaviridae family.

	Drug 2 Target							
Drug 1 Target	Human (multiple); Viral protease	Human DHODH	Human OSBP	N/A	Viral protease	Viral RNA pol	Viral VP1	Total
Human OSBP					1			1
N/A		1	1	33	4	2	1	42
Viral DNA pol;Viral RNA pol;Viral RT						2		2
Viral protease	1			3				4
Viral RNA pol	1		1	1	2			5
Total	2	1	2	37	7	4	1	54

The mode of action (MoA) may influence the synergy prediction in drug combinations. Out of 770 combinations with any positive effects, 8 AVCs share the same MoA. Among these, 2 are in phase 3 clinical trials, and 3 have been tested in animal studies. The remaining have different MOAs.

When examining combinations that produce negative effects, such as antagonistic or no effect, it is observed that antagonistic drug combinations are most prevalent in those targeting virus components, such as viral RNA polymerase, as illustrated in Table 7. This high number may be attributed to the database's large number of RNA viruses.

Table 7 presents the drug targets of combinations exhibiting no effect or antagonistic effects, focusing specifically on combinations targeting virus components.

	Unknown;Viral neuraminidase	Unknown;Viral protease	Viral DNA pol	Viral DNA pol;Viral RNA pol	Viral DNA pol;Viral RNA pol;Viral RT	Viral DNA pol;Viral RT	Viral NS5A	Viral protease	Viral protease;Human protease	Viral RNA pol	Viral RT
Unknown;Viral protease		1									
Unknown;Viral neuraminidase											
Viral DNA pol											
Viral DNA pol;Viral RNA pol;Viral RT				1							
Viral DNA pol;Viral RNA pol;Viral RT				1							
Viral protease					1						
Viral RNA pol				1			1		2	2	
Viral RT											

4.1.3 Integration of the AVDC Database into the DrugVirus.info Database

In the DrugVirus.info database, the initial number of BCCs was 540. However, after removing 4 duplicates, 536 BCCs remained. Subsequently, these BCCs were combined with additional combinations from the AVDC database to create an expanded list of combinations. A total of 318 new combinations were incorporated into DrugVirus.info, resulting in an updated database containing 854 combinations. The names of drugs, viruses, and cell cultures were standardized to avoid duplicate entries.

4.2 Antiviral drug combination against EV-1 in A549 cells

Identifying potential drug candidates is of utmost importance considering the lack of approved therapies for enterovirus infections [22]. In this study, in vitro screening was performed on identified drugs used in combinations and added to the AVDC database, except for IMP-1088. Five drugs, namely enviroxime, dipyridamole, sangivamycin, vapendavir, and IMP-1088, were effective against EV-1. Notably, when this thesis was being written, IMP-1088 had not been used

in combination. The in vitro screening also provided information on effective concentration ranges against the EV-1 virus in A549 cells with acceptable toxicity levels. Moreover, several drugs previously investigated by the research group and found effective against EV-1, including emetine, vemurafenib, pleconaril, rupintrivir, remdesivir, cycloheximide, and anisomycin, were included in the study to explore if their combinations yielded any additional benefits [22].

The antiviral effects of twelve drugs were evaluated against EV-1 in A549 cells, testing various concentrations and combinations to determine their impact on the virus. A total of 21 combinations exhibited synergistic effects, 33 combinations showed additive effects, and 3 combinations resulted in antagonistic effects. Antagonistic effects were observed across all tested concentration ranges for the combinations of remdesivir and pleconaril plus vapendavir, enviroxime plus vemurafenib, as depicted in Figure 6.

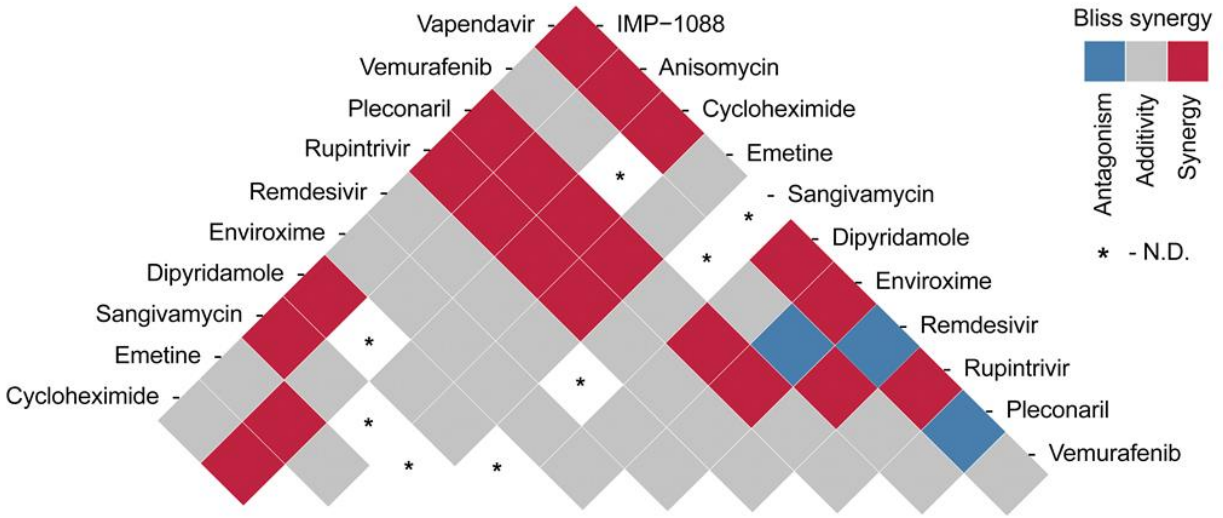


Figure 6 depicts drug combinations tested against the EV-1 virus in A549 cells. Cells were exposed to increasing concentrations of drug combinations and infected with EV1 or a mock sample. After 48 hours,

the viability of virus- and mock-infected cells was assessed using a CTG assay. The selectivity for the drugs was determined (selectivity = efficacy - (100 - Toxicity)). BLISS synergy scores were calculated for the most synergistic regions, with scores greater than or equal to 10 indicating synergy, scores between 0 and 9 signifying additivity, and scores less than 0 representing antagonism. Synergy is represented by red, additivity by grey and antagonism by blue. Combinations displaying synergistic effects at any concentration are considered synergistic, while antagonism is recognized if a combination exhibits antagonistic effects at the highest achieved effect. N.D. refers to cases where the therapeutic window was too low to calculate the synergy score (viability of drug-treated infected cells was below 75%).

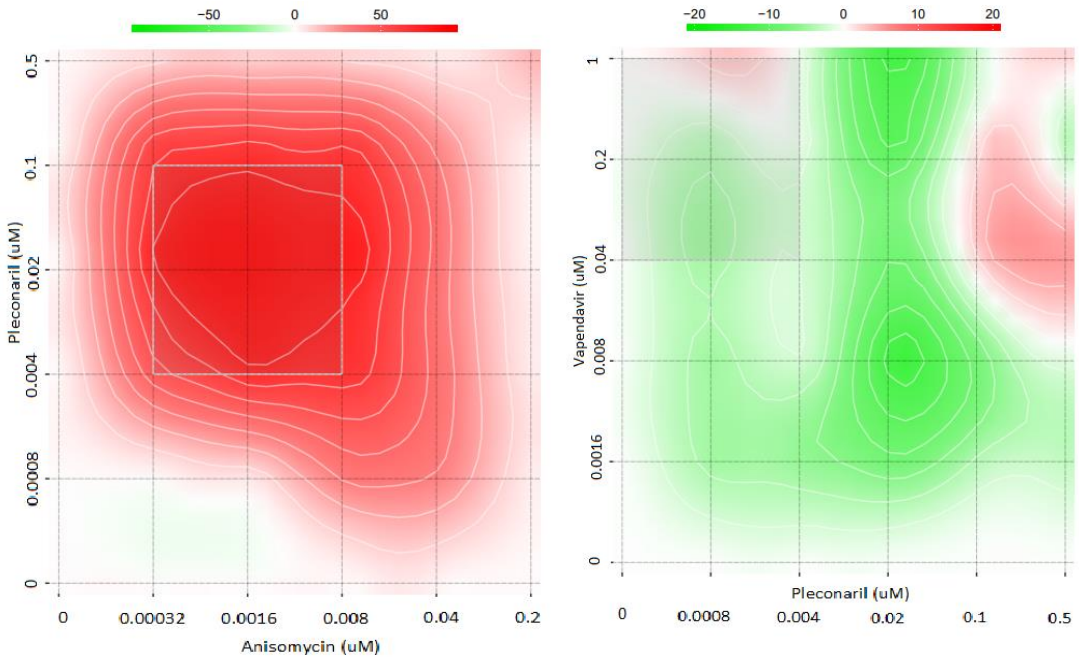


Figure 7 presents the interaction landscape, which depicts the synergistic effect of the pleconaril and anisomycin combination on the left side, and the antagonistic effect of the pleconaril and vapendavir combination on the right side.

Pleconaril is a small-molecule inhibitor that is effective against enteroviruses and rhinoviruses belonging to the Picornaviridae family. Its mechanism of action involves inhibiting the uncoating of the viral RNA genome [26]. In the experiment, pleconaril demonstrated the highest number of synergistic drug combinations. The combination of pleconaril and anisomycin, an antibiotic that interferes with protein and DNA synthesis [27], achieved the highest synergistic score with a most synergistic area (MSA) of 68. Anisomycin has previously been effective against

EV-1 in vitro when combined with other drugs by the research group [22]. The combination of pleconaril and cycloheximide, an antibiotic [28], yielded a synergy score of 66 MSA. In contrast, the combination with enviroxime, a drug that inhibits viral proteins involved in viral RNA replication and suppresses EV infection [29], obtained a synergy score of 48 MSA.

Conversely, the combinations of vapendavir with pleconaril or remdesivir exhibited antagonistic effects, with MSA values of -1 and -0.7, respectively. The combination of vemurafenib and enviroxime also displayed an antagonistic effect, with an MSA of -0.6.

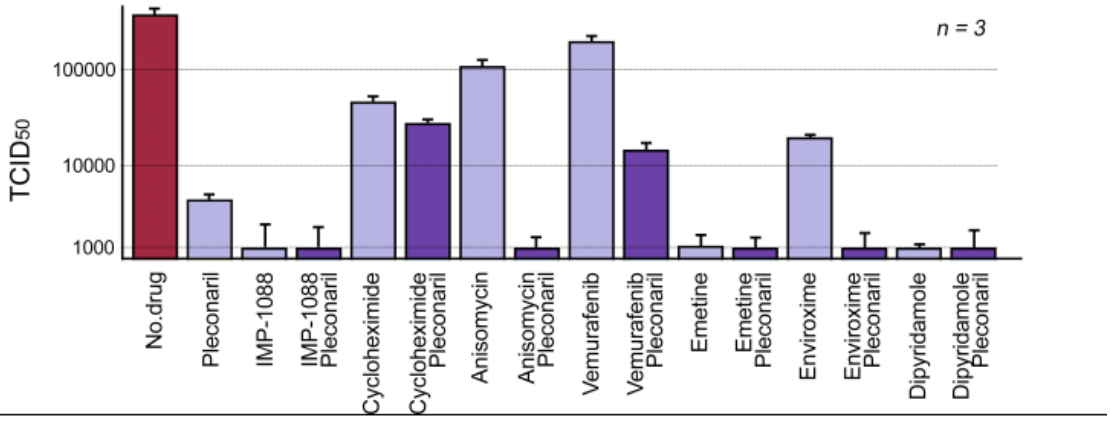


Figure 8 displays the TCID50 (Median Tissue Culture Infectious Dose) range from 10^{-3} to 10^{-5} dilutions for various drug samples assessed in A549 cells with the EV-1 virus. This encompasses the TCID50 of samples with no drug, mono drugs such as pleconaril, IMP-1088, cycloheximide, anisomycin, vemurafenib, emetine, enviroxime, and dipyridamole, as well as combinations of these drugs with pleconaril.

Pleconaril was further assessed using a TCID50 assay, which measures the amount of virus needed to cause a cytopathic effect or visible damage in 50% of the cells in cell culture. This assay relies on the dilution of a virus stock [30], and the addition of a drug or drug combination allows for the observation of changes in TCID50 values. This method can be utilized to examine the effects of drug combinations. In this virus titer experiment, pleconaril was combined with IMP-1088, cycloheximide, anisomycin, vemurafenib, emetine, enviroxime, and dipyridamole. Wells without drugs exhibited the highest dilution values, suggesting that a small quantity of the virus was sufficient to damage 50% of the cell culture. Concurrently, pleconaril combined with anisomycin, vemurafenib, and enviroxime demonstrated significant reductions in TCID50

compared to the TCID50 of the drugs tested individually, potentially indicating that pleconaril enhances their antiviral effects. For several drugs, such as IMP-1088, emetine, and dipyridamole, low TCID50 values were observed when tested alone, making it challenging to determine if pleconaril improves the antiviral effect of these combinations through this experiment.

Discussion

The recent pandemic has underscored the significance of being prepared with political, social, and medical strategies to mitigate high mortality rates. In this thesis, data on antiviral drug combinations, including approved and potentially approvable ones, was collected. The AVDC database expanded by 261 new combinations, resulting in a 29.3% increase from its initial size. After removing duplicates and combinations found in advanced clinical phases, the database now contains 980 combinations.

The database is dominated by SARS-CoV-2 targeting combinations, increasing from 47 to 139 combinations after expansion. This might be attributed to the high research interest in COVID-19 or the database development occurring during the pandemic, with drug combinations being explored as potential treatments.

Reviewing older articles to discover previously unidentified antiviral combinations could yield valuable insights. However, for this thesis, unique combinations were incorporated into the database. Unique combinations are defined as those with specific drugs, cell lines, clinical states, or viruses to prevent data inflation, and references for removed combinations were preserved. This approach was taken due to the focus on identifying previously tested new combinations and the attempt to discover novel combinations. Simultaneously, it may make statistical analysis more difficult, as some data has been removed, and the exact number of combinations needs to be present. Another factor to consider is the continuous improvements in methods and experimental equipment, which could influence the results of identical combinations and potentially introduce inaccuracies during analysis.

With the database's expansion, drug combinations' effects were documented to explore potential associations between drug properties and antiviral effect prediction. Out of the combinations producing positive effects, 129 targeted viral components with both drugs, 79 involved one drug targeting a viral component and the other a human component, and 27 had both drugs targeting human components. The overrepresentation of virus-virus and virus-host targeting BCCs suggests that drugs specifically developed to target viral factors may be more successful in achieving a direct antiviral effect while minimizing severe side effects. On the other hand, host-host targeting

of AVCs poses a lower risk of drug resistance and offers a broader spectrum of antiviral activity [14].

In antiviral drug combinations, synergistic effects are more likely to occur when the drugs belong to different classes, possess independent mechanisms of action, or target different stages of the virus life cycle [31]. This observation aligns with a developed formula that considers the mechanism of action for each component, drug target interaction, stage of replication targeted, and the administration route [14]. Consistent with this, out of 770 combinations exhibiting positive effects, only 8 combinations share the same mechanism of action. Combinations targeting virus-virus interactions have been predominant among effective combinations. However, it is important to note that the high number of unknown drug targets may influence these results.

The method of obtaining new drug combinations is crucial. Search terms such as "antiviral combinations," "synergistic and antiviral combination," and "antagonism and antiviral combination" were utilized to cover a significant portion of articles published in 2022. Searches were conducted on PubMed and ClinicalTrials.org. A more comprehensive search in other databases could have yielded more results for the database expansion, but time constraints limited the search scope. Data were primarily reviewed and collected by a single individual, and although there were clear criteria for data collection, including drug names and their effects, having an additional person to review and compare the collected data could have been beneficial. This collaborative approach could have ensured greater accuracy in the data and facilitated discussions in case of disagreements.

This thesis examined drug combinations in A549 cells, either mock-infected or infected with EV1 for 48 hours, to ascertain if any combinations produced beneficial outcomes, such as synergistic or additive effects. Synergistic combinations utilize lower concentrations of antiviral agents, potentially reducing toxicity and side effects. Furthermore, employing BCCs may help address antiviral resistance, a significant challenge in treating viral infections [13]. The Norwegian Institute of Public Health (NIPH) published a report in 2022 on antiviral drug usage and the emergence of antiviral resistance in Norway in 2021[32]. The report identified resistance to ganciclovir and maribavir against cytomegalovirus and baloxavir marboxil against the influenza virus. Adamantanes, previously used against the influenza virus, are now encountering resistant

circulating influenza viruses. As a result, these antivirals are no longer utilized for treatment in Norway and most other countries [32].

The findings suggest that numerous drug combinations exhibited a synergistic effect against EV-1. When combined with anisomycin, pleconaril displays the highest synergistic area (67.85). However, despite pleconaril's good effect in combination with other antiviral drugs, its solo use in clinical trials for enterovirus infection has not succeeded due to its limited efficacy and side effects [22]

Anisomycin, an antibiotic, has been tested against various viruses, including dengue, zika, coronavirus, and poliovirus [33][34][35]. In vitro studies have demonstrated promising antiviral effects of anisomycin against these single-stranded, positive-sense RNA viruses [36]. The virus titration in this study revealed a significant reduction in the TCID50 value of pleconaril combined with anisomycin against EV-1 in A549 cells compared to anisomycin alone, decreasing from 10^{-5} to 10^{-3}. This confirms the synergistic effect of this drug combination. It can be inferred that the drug combinations are more effective at inhibiting virus replication and spread to other cells since a higher concentration of the virus is needed to infect 50% of the cells in the A549 cell culture.

This study's findings reveal Three combinations displaying antagonistic effects: pleconaril or remdesivir plus vapendavir, and enviroxime plus vemurafenib. Vapendavir, a capsid binder used to treat rhinovirus infections [37], has also been tested for effective inhibition of EV71 replication in vitro [38]. A previous in vitro study investigating the combination of vapendavir, rupintrivir, and enviroxime against poliovirus 1, enterovirus 71 (EV-71), and rhinovirus 14 (HRV-B14)—all part of the same family of positive-sense, single-stranded RNA viruses—primarily exhibited synergistic effects, with a few antagonistic concentration areas [39]. The unexpected antagonistic effect observed when pleconaril is combined with vapendavir (SI -3.7 and MSA -1.01) is surprising.

Remdesivir, a prodrug of an adenosine nucleotide analog, requires metabolism within host cells to form an active nucleotide triphosphate and functions by inhibiting viral RNA. It has been utilized in the treatment of SARS-CoV-2 [40]. In vitro tests have demonstrated the antiviral effects of

remdesivir against enteroviruses EV-71 [41] and EV-1 [22]. However, surprisingly, the combination of remdesivir and vapendavir has exhibited antagonistic effects.

Possible factors leading to the observed antagonistic effect include target competition, opposing mechanisms, or chemical interactions. With values close to the threshold for additive effects, it is challenging to rule out human error or practical issues contributing to the antagonistic outcome. Determining the exact cause of this antagonistic effect is complex and may result from a combination of these factors. Conducting virus titer experiments on these combinations could have helped confirm or refute the human error hypothesis. A decrease in TCID 50 would be expected if the combinations were effective.

This thesis has successfully identified novel drug combinations not previously tested in vitro against EV-1. Through extensive experimentation, it was found that many of these drug combinations exhibit synergistic effects, suggesting potential for further investigation. It is important to note that the results of this thesis may differ when tested in vivo due to various factors such as specificity, metabolism, pharmacokinetics, drug interactions, and biological variability. Nevertheless, the findings of this experiment still offer valuable information for future research in this field.

Conclusion

The recent pandemic has highlighted the crucial need for preparedness in the face of unpredictable viral outbreaks and the extensive consequences they can bring. Ensuring effective and timely responses is vital to minimize the impact on public health and society. In this thesis, the AntiViralDualCombi database was expanded, contributing to the update of the DrugVirus database. This thorough literature review will be valuable for researchers interested in antiviral properties and potential treatment approaches. Through this research, novel BCCs exhibiting potential antiviral properties against EV-1 were discovered, paving the way for further investigations in diverse experimental settings, such as in vivo studies and clinical trials. The possibility of repurposing existing drugs and investigating their synergistic effects when combined was also emphasized, which could aid in developing more effective treatments and enhanced preparedness for future viral outbreaks.

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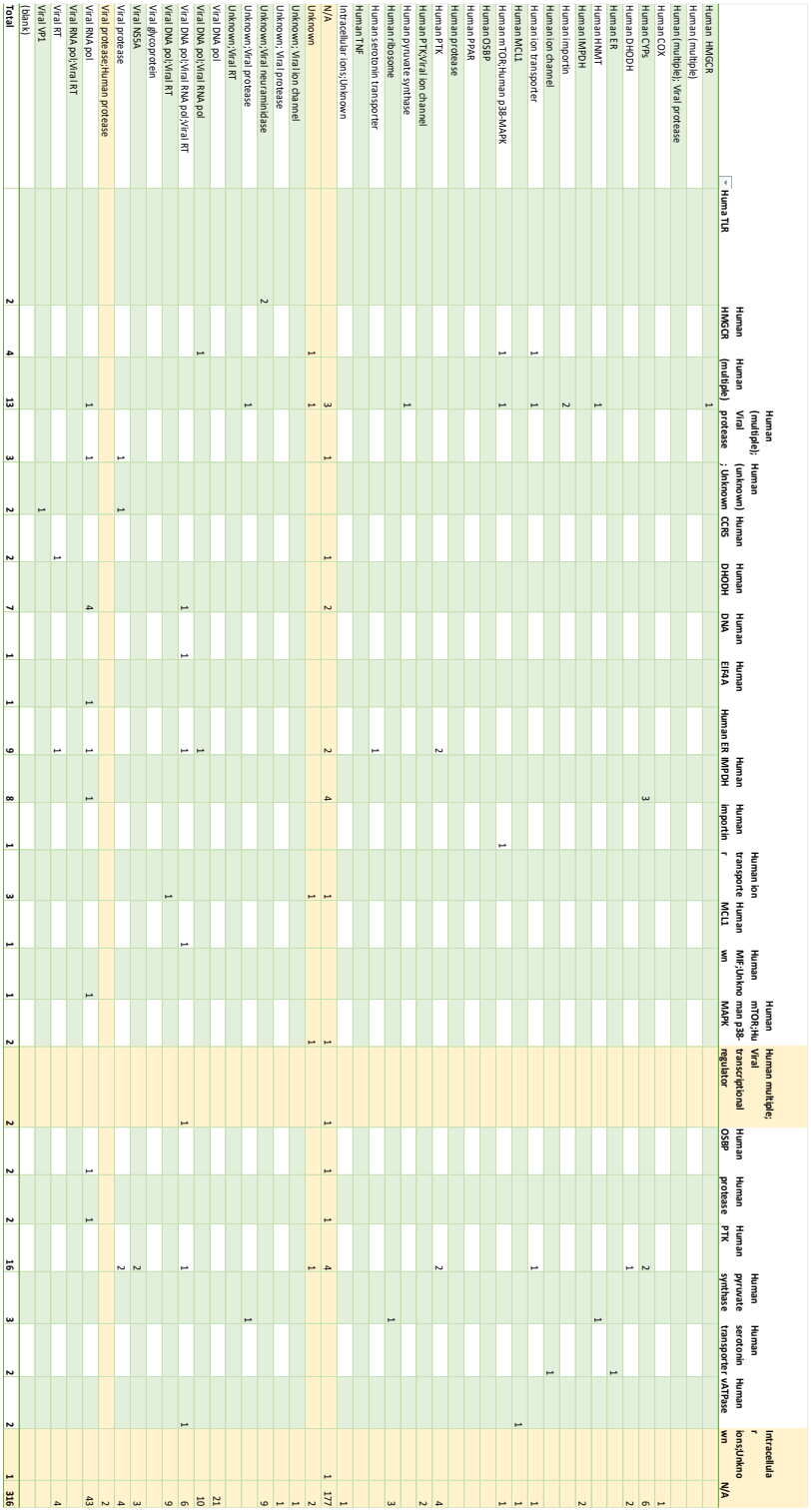
Appendix A - Drugs utilized in this thesis

Table A presents the drugs employed in the experiments, including the supplier, catalog number, formula, and other relevant details about the drugs.

Drug	CAS	Brand	Purity (%)	Cat. #	Formula	MW
Vapendavir diphosphate	1198151-75-5	MedChemExpress	98,8 %	HY-106254A	C21H32N4O11P2	578,5
Dipyridamole	58-32-2	Sigma-Aldrich	≥98	D9766	C24H40N8O4	504,6
Enviroxime	72301-79-2	Cayman Chemical	≥95	30552-1	C12H11N3O2	241,2
Sangivamycin	18417-89-5	MedChemExpress	97,1 %	HY-118384	C19H27N7O5	471,4
IMP-1088	2059148-82-0	MedChemExpress	98,8 %	HY-112258	C21H24N4O3	376,4
Emetine	7083-71-8	Cayman Chemical	>98	21048	C29H40N2O4	480,6
Vemurafenib	918504-65-1	MedChemExpress	99,8 %	HY-12057	C23H18ClF2N3O3S	489,9
Pleconaril	153168-05-9	Cayman Chemical	≥98	28461	C19H20FNO3	323,3
Rupintrivir	223537-30-2	Sigma-Aldrich	≥98	PZ0315	C27H32N4O3	481,5
Remdesivir	1809249-37-3	Cayman Chemical	>98	30354	C27H35N6O8P	602,6
Anisomycin	22862-76-6	Sigma-Aldrich	>98	A9789	C14H19NO4	265,3
Cycloheximide	86-81-9	Sigma-Aldrich	>94	C7698	C15H23NO4	281,4

Supplementary

Table S.1 displays the drug targets of drug combinations that exhibit positive effects.



Human TR	Human HMGCR	Human (multiple)	Human (multiple); Viral protease	Human ; Unknown	Human CCR5	Human DHODH	Human DNA	Human EIF4A	Human ER	Human IMPDH	Human importin	Human ion transporte r	Human MCL1	Human MIF;Unkno wn	Human mTOR;Hu man p38-MAPK	Human multiple; Viral transcriptional regulator	Human OSBP	Human protease	Human PTK	Human pyruvate synthase	Human serotonin transporter	Human vATPase	Intracellula r ions;Unkno wn	N/A	
Human HMGCR																								
Human (multiple)		1																						
Human (multiple); Viral protease																								
Human COX																								
Human CYPs																			2					1
Human DHODH									3										1					6
Human ER																								2
Human HMAT			1																	1				
Human IMPDH																					1			
Human importin			2																					2
Human ion transporter													1											
Human MCL1		1	1																1			1		1
Human mTOR;Human p38-MAPK											1												1	1
Human OSBP		1	1																					1
Human PPAR																								
Human protease																			2					4
Human PTK									2															2
Human PTK/Viral ion channel																								
Human pyruvate synthase			1																		1			3
Human ribosome																								
Human serotonin transporter									1															
Human TNF																								1
Intracellular ions;Unknown																								1
N/A			3	1		1	2		2	4		1		1	1	1	1	1	4				1	177
Unknown		1	1									1			1				1					2
Unknown; Viral ion channel																								1
Unknown; Viral protease																								1
Unknown;Viral neuraminidase		2																						9
Unknown;Viral protease			1																		1			
Unknown;Viral RT																								
Viral DNA pol									1															21
Viral DNA pol;Viral RNA pol		1					1	1		1				1									1	10
Viral DNA pol;Viral RNA pol/Viral RT												1			1	1			1					6
Viral DNA pol;Viral RT																								9
Viral gPcoprotein																								
Viral NS5A					1															2				3
Viral protease																				2				4
Viral protease;Human protease																	1	1	1					2
Viral RNA pol			1		1		4		1	1				1			1	1						43
Viral RNA pol/Viral RT																								
Viral RT						1				1														4
Viral VPr				1																				
(blank)																								
Total	2	4	13	3	2	2	7	1	1	9	8	1	3	1	2	2	2	2	16	3	2	2	1	316

Unknown	Unknown; Viral ion channel	Unknown; Viral neuraminidase	Unknown; Viral protease	Unknown; Viral neuraminidase	Unknown; Viral protease	Viral DNA pol	Viral DNA pol; Viral RNA pol	Viral DNA pol; Viral RNA pol; Viral RT	Viral DNA pol; Viral RT	Viral DNA pol;Viral RNA pol	Viral DNA pol;Viral RNA pol;Viral RT	Viral DNA pol;Viral RT	Viral glycoprotein	Viral NS5A	Viral protease	Viral RNA pol	Viral RNA pol; Viral RT	Viral RNA pol;Viral RT	Viral RT	Viral VP1	(blank)	Total
																						1
					1											1						2
		1																				1
																						1
												1		1	1	4						18
																2						5
								1														2
1					1											1						5
																5						7
																1						3
																						1
												1										5
																						2
																1						5
															1							1
				1																		1
																2						2
1															2	2						13
																						2
		1		1												2						5
															1							6
																						1
								1								1						2
																						1
1	3	4		16		16	11	7		7	16	5		1	7	77	2		4	1		378
								1		1	1	1			1	3						15
																						1
									1													2
	1	1														3						16
			1													1						4
											1											1
2						7	7	2		3	7		4			1						54
						2		1			2	1							1			19
							2	2			1	6				2						26
								2	1		2											15
						1	1				1					1						4
											1				1	6						13
			2											1		2		1				14
	1															4						7
1	2	1		1				1			1				4	16			1			83
								1														1
				2		2		1			5	1				3			3			23
															1							2
6	7	8	3	21	2	28	21	20	2	11	38	16	4	3	20	141	2	1	9	1		770

Table S.2 displays the targets of drug combinations exhibiting negative effects.

	Human (multiple)	Human CYPs	Human MCL1	Human OSBP	Human PPAR	Human ribosome	N/A	Unknown	Unknown;Viral neuraminidase	Unknown;Viral protease	Viral DNA pol	Viral DNA pol/Viral RNA pol	Viral DNA pol/Viral RNA pol/Viral RT	Viral DNA pol/Viral RT	Viral NSA	Viral protease	Viral protease;Human protease	Viral RNA pol	Viral RT	Total
Human HMGCR					1				1											2
Human (multiple); Viral protease			1	1																1
Human COX							1													1
Human IMPDH							1													1
N/A						1	10			1	1	1	1	4	1	1		1	1	20
Unknown;Viral protease										1										1
Unknown;Viral neuraminidase							4	1												5
Viral DNA pol							1											1		1
Viral DNA pol/ Viral RNA pol/ Viral RT							1					1								2
Viral DNA pol/Viral RNA pol/Viral RT			1			1	1				1		1							2
Viral protease	1						2					1					2			6
Viral RNA pol	1	1					6								1			2		14
Viral RT							2												1	2
Total	**2**	**1**	**1**	**1**	**1**	**1**	**29**	**1**	**1**	**1**	**1**	**4**	**2**	**4**	**1**	**1**	**2**	**3**	**1**	**58**

S.3 AVDC Database

Table S.3 presents the AVDC database with drug combinations, clinical phases, references, and relevant details. It also includes information on the effects of the drug combinations.

NR.	Virus	Drug 1	Drug 2	Clinical phase	Cell line/animal model	Reference	Synergist	Additive	Antagonistic	No effe	Positive	No relevant
1	HSV-1	(22S;23S)-3Beta-Bromo-5Alpha;22;23-Trihydroxystigmastan-6-One	Foscarnet	Preclinical	Vero cell	PMID:16340198	x					
2	SARS-CoV	(23;25)Trans-Epoxysuccinyl-L-Leucylamindo-3-Methylbutaneethylester(est)	Camostat	Preclinical	Hela cell	PMID:22496216					x	
3	HBV	1C8	Pam3CSK4	Preclinical	PHH;HepaRG cell	PMID:35963549					x	
4	PV-1	2´-C-Methylcytidine	Ribavirin	Preclinical	Unknown	PMID:21466823	x		x			
5	PV-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Arildone	Preclinical	FL cell	PMID:10757231	x	x				
6	CVB-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Arildone	Preclinical	Cell culture	PMID:15026197	x					
7	PV-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Disoxaril	Preclinical	FL cell	PMID:10757231	x					
8	CVB-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Disoxaril	Preclinical	Cell culture	PMID:15026197	x					
9	PV-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Preclinical	FL cell	PMID:10757231	x					
10	CVB-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Preclinical	Cell culture	PMID:15026197	x					
11	CVB-1	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Guanidine	Preclinical	FL cell	PMID:10757231	x	x				
12	HBV	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Guanidine	Preclinical	Mice	PMID:1271013					x	
13	HRV-A9	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Guanidine	Preclinical	Mice	PMID:1271013					x	
14	HRV-A9	2-Alpha-Hydroxybenzyl-Benzimidazole(Hbb)	Guanidine	Preclinical	Mice	PMID:6299189					x	
15	CMV	2-Bromo-5,6-Dichloro-1-Beta-D-Ribofuranosylbenzimidazoleriboside(Bdcrb)	Brincidofovir	Preclinical	HFF cell	PMID:30153445	x					
16	CMV	2-Bromo-5,6-Dichloro-1-Beta-D-Ribofuranosylbenzimidazoleriboside(Bdcrb)	Cidofovir	Preclinical	HFF cell	PMID:30153445	x					
17	CMV	2-Bromo-5,6-Dichloro-1-Beta-D-Ribofuranosylbenzimidazoleriboside(Bdcrb)	Cyclopropavir	Preclinical	HFF cell	PMID:30153445	x					
18	CMV	2-Bromo-5,6-Dichloro-1-Beta-D-Ribofuranosylbenzimidazoleriboside(Bdcrb)	Ganciclovir	Preclinical	HFF cell	PMID:30153445	x					
19	HCV	2'-C-Methylcytidine	Chlorcyclizine	Preclinical	Huh-7.5.1;Con1b cell	PMID:27035622	x					
20	HEV	2'-C-Methylcytidine	Ribavirin	Preclinical	PLC/PRF/5 cell	PMID:31362004		x				
21	NoV	2'-C-Methylcytidine	Rupintrivir	Preclinical	HG23 Cell	PMID:24890597		x				
22	HCV	2'-C-Methylcytidine	Sofosbuvir	Preclinical	Huh-7 cell	PMID:27035622	x	x				
23	HCV	2'-C-Methylcytidine	Tegobuvir	Preclinical	Huh-9-13;Huh-6;Huh5-2 cell	PMID:26036224		x				
24	HEV	2'-C-Methylguanine	Interferon Alpha	Preclinical	PLC/PRF/5 cell	PMID:31362004		x				
25	HEV	2'-C-Methylguanine	Interferon Beta	Preclinical	PLC/PRF/5 cell	PMID:31362004		x				
26	HEV	2'-C-Methylguanine	Ribavirin	Preclinical	PLC/PRF/5 cell	PMID:31362004		x				
27	HSV-2	2'-Fluoro-5-Iodoaracytosine(Fiac)	Vidarabine	Preclinical	Mice	PMID:3777913	x					
28	HSV-2	2'-Fluoro-5-Methylarauracil(Fmau)	Vidarabine	Preclinical	Mice	PMID:3777913	x					
29	HRV-A9	2-Guanidino-Benzimidazole(Gb)	Guanidine	Preclinical	Mice	PMID:6299189					x	
30	HSV-1	2-Phenylamino-6-Oxo-9-(4-Hydroxybutyl)Purine(Hbpg)	Acyclovir	Preclinical	Mice	PMID:20054446	x					
31	HSV-1	2-Phenylamino-6-Oxo-9-(4-Hydroxybutyl)Purine(Hbpg)	Cidofovir	Preclinical	Mice	PMID:20054446		x				
32	HSV-2	2-Phenylamino-6-Oxo-9-(4-Hydroxybutyl)Purine(Hbpg)	Cidofovir	Preclinical	Mice	PMID:20054446		x				
33	HSV-2	2-Phenylamino-6-Oxo-9-(4-Hydroxybutyl)Purine(Hbpg)	Foscarnet	Preclinical	Mice	PMID:20054446		x				
34	HSV-1	2-Phenylamino-6-Oxo-9-(4-Hydroxybutyl)Purine(Hbpg)	Interferon Beta	Preclinical	Vero cell	PMID:2163462	x					
35	HSV-1	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Edoxudine	Preclinical	RK-13; Vero cell	PMID:6249191			x			
36	HSV-1	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Foscarnet	Preclinical	RK-13 cell	PMID:2984988	x					
37	HSV-2	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Foscarnet	Preclinical	RK-13 cell	PMID:2984988	x					
38	HSV-1	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Idoxuridine	Preclinical	RK-13; Vero cell	PMID:6249191			x			
39	HSV-1	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Phosphonoacetic Acid	Preclinical	RK-13; Vero cell	PMID:6249191	x					

40	HSV-1	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Trifluridine	Preclinical	RK-13 cell	PMID:2984988	x					
41	HSV-2	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Trifluridine	Preclinical	RK-13 cell	PMID:2984988	x					
42	HSV-1	5-Methoxymethyl-2'-Deoxyuridine(Mmudr)	Vidarabine	Preclinical	RK-13; Vero cell	PMID:6249191	x					
43	VACV	5-Methyltryptophan	Broxuridine	Preclinical	Unknown	PMID:14231461					x	
44	HSV-1	5-Trifluorothymidine(Tft)	Acyclovir	Preclinical	Vero cell	PMID:6285731		x				
45	HSV-2	5-Trifluorothymidine(Tft)	Acyclovir	Preclinical	Vero cell	PMID:6285731		x				
46	VZV	5-Trifluorothymidine(Tft)	Acyclovir	Preclinical	WI-38 cell	PMID:6285731		x				
47	VZV	5-Trifluorothymidine(Tft)	Acyclovir	Preclinical	MRC-5 cell	PMID:6285733		x				
48	HSV-1	5-Trifluorothymidine(Tft)	Brivudine	Preclinical	Vero cell	PMID:6285731		x				
49	HSV-2	5-Trifluorothymidine(Tft)	Brivudine	Preclinical	Vero cell	PMID:6285731		x				
50	HSV-1	5-Trifluorothymidine(Tft)	Foscarnet	Preclinical	Vero cell	PMID:6285731		x				
51	HSV-2	5-Trifluorothymidine(Tft)	Foscarnet	Preclinical	Vero cell	PMID:6285731		x				
52	HSV-1	5-Trifluorothymidine(Tft)	Vidarabine	Preclinical	Vero cell	PMID:6285731	x					
53	HSV-2	5-Trifluorothymidine(Tft)	Vidarabine	Preclinical	Vero cell	PMID:6285731	x					
54	FLUAV	6'SLN-CD	Interferon Lambda	Preclinical	HAE cell	PMID:36216966	x					
55	SARS-CoV-2	7-Hydroxystaurosporine	Bafetinib	Preclinical	HEK293 cell	PMID:34962256	x					
56	HSV-2	9-(1,3-Dihydroxy-2-Propoxymethyl)Guanine(Dhpg)	Interferon Beta	Preclinical	Mice	PMID:6610387	x					
57	HBV	AB-506	Antibodies	Preclinical	HepDE19 cell	PMID:34826506		x				
58	HBV	AB-506	Entecavir	Preclinical	HepDE19 cell	PMID:34826506		x				
59	HBV	AB-506	Tenofovir Alafenamide	Preclinical	HepDE19 cell	PMID:34826506	x					
60	HBV	AB-506	Tenofovir Disproxil fumarate	Preclinical	HepDE19 cell	PMID:34826506		x				
61	HIV-1	Abacavir	Amprenavir	2	Human	NCT00002440						N/A
62	HIV-1	Abacavir	Indinavir	2	Human	NCT00002440						N/A
63	HIV-1	Abacavir	Nelfinavir	2	Human	NCT00002440						N/A
64	HIV-1	Abacavir	Ritonavir	2	Human	NCT00002440						N/A
65	HIV-1	Abacavir	Saquinavir	2	Human	NCT00002440						N/A
66	HBV	ABI-H0731	Entecavir	2	Human	NCT03576066					x	
67	HBV	ABI-H0731	Tenofovir	2	Human	NCT03576066					x	
68	HIV-1	Acemannan	Acyclovir	Preclinical	Unknown	PMID:1662957	x					
69	HSV-1	Acemannan	Acyclovir	Preclinical	Unknown	PMID:1662957	x					
70	HIV-1	Acemannan	Zidovudine	Preclinical	Unknown	PMID:1662957	x					
71	HSV-1	Acemannan	Zidovudine	Preclinical	Unknown	PMID:1662957	x					
72	VZV	Acyclovir	Amenamevir	Preclinical	MRC-5 cell	PMID:23261844	x					
73	HSV-2	Acyclovir	Amenamevir	Preclinical	Vero cell	PMID:23261844	x					
74	HSV-1	Acyclovir	Amenamevir	Preclinical	Vero;HFF cell	PMID:23261844	x					
75	HSV-2	Acyclovir	Amenamevir	Preclinical	Vero;HFF cell	PMID:23261844	x					
76	VZV	Acyclovir	Amenamevir	Preclinical	Vero;HFF cell	PMID:23261844	x					
77	HSV-1	Acyclovir	Antibodies	Preclinical	Vero cell	PMID:29357297	x					
78	HSV-2	Acyclovir	Antibodies	Preclinical	Vero cell	PMID:29357297	x		x			
79	HSV-1	Acyclovir	Aphidicolin	Preclinical	Vero cell	PMID:12087926	x					
80	HHV-1	Acyclovir	Bosutinib	Preclinical	Vero cell	PMID:35238349	x		x			
81	HSV-1	Acyclovir	Brincidofovir	Preclinical	Mice	PMID:21788472	x					
82	HSV-2	Acyclovir	Brincidofovir	Preclinical	Mice	PMID:21788472	x					
83	HSV-1	Acyclovir	Brivudine	Preclinical	Vero cell	PMID:6285731		x				
84	HSV-2	Acyclovir	Brivudine	Preclinical	Vero cell	PMID:6285731		x				
85	VZV	Acyclovir	Brivudine	Preclinical	WI-38 cell	PMID:6285731		x				
86	VZV	Acyclovir	Brivudine	Preclinical	MRC-5 cell	PMID:6285733		x				
87	HSV-1	Acyclovir	Carbocyclic Oxetanocin G	Preclinical	Vero cell	PMID:1333651		x				
88	HSV-2	Acyclovir	Carbocyclic Oxetanocin G	Preclinical	Vero cell	PMID:1333651		x				
89	CMV	Acyclovir	Cidofovir	Preclinical	HEL cell	PMID:1337893	x	x				
90	CMV	Acyclovir	Docosanol	Preclinical	MRC-5 cell	PMID:12367721	x					
91	VZV	Acyclovir	Docosanol	Preclinical	MRC-5 cell	PMID:12367721	x					
92	HSV-1	Acyclovir	Docosanol	Preclinical	Vero cell	PMID:12367721	x					
93	HSV-2	Acyclovir	Docosanol	Preclinical	Vero cell	PMID:12367721	x					
94	HSV-1	Acyclovir	Foscarnet	0/1	Human	PMID:30652455					x	
95	CMV	Acyclovir	Foscarnet	Preclinical	HEL cell	PMID:6179416	x					
96	HSV-1	Acyclovir	Foscarnet	Preclinical	Vero cell	PMID:6285731		x				
97	HSV-2	Acyclovir	Foscarnet	Preclinical	Vero cell	PMID:6285731		x				
98	VZV	Acyclovir	Foscarnet	Preclinical	WI-38 cell	PMID:6285731		x				
99	VZV	Acyclovir	Foscarnet	N/A	Human	PMID:32815746						x
100	VZV	Acyclovir	Idoxuridine	Preclinical	WI-38 cell	PMID:6285731		x				
101	VZV	Acyclovir	Idoxuridine	Preclinical	MRC-5 cell	PMID:6285733		x				
102	HSV-1	Acyclovir	Interferon Alpha	Preclinical	Unknown	PMID:2987369	x					
103	HSV-2	Acyclovir	Interferon Alpha	Preclinical	Unknown	PMID:2987369	x					
104	HSV-1	Acyclovir	Interferon Beta	Preclinical	Vero cell	PMID:2163462	x					
105	CMV	Acyclovir	Lactoferrin	Preclinical	Flf	PMID:12742576			x			
106	CMV	Acyclovir	Letermovir	Preclinical	NHDF cell	PMID:25779572		x				
107	HSV-1	Acyclovir	Omeprazole	Preclinical	HaCat; Vero cell	PMID:31849920					x	
108	HSV-2	Acyclovir	Omeprazole	Preclinical	HaCat; Vero cell	PMID:31849920					x	
109	HSV-1	Acyclovir	Oxetanocin G	Preclinical	Vero cell	PMID:1333651	x					
110	HSV-2	Acyclovir	Oxetanocin G	Preclinical	Vero cell	PMID:1333651	x					
111	HSV-1	Acyclovir	Quercetin	Preclinical	Cef cell	PMID:1339152	x					
112	HSV-2	Acyclovir	Quercetin	Preclinical	Cef cell	PMID:1339152	x					
113	HSV-1	Acyclovir	Ribavirin	Preclinical	Unknown	PMID:2166426	x					
114	CMV	Acyclovir	Trifluridine	Preclinical	HEL cell	PMID:6179416	x					
115	HSV-2	Acyclovir	Vidarabine	Preclinical	Mice	PMID:2455473					x	
116	HSV-1	Acyclovir	Vidarabine	Preclinical	Vero cell	PMID:6285731		x				
117	HSV-2	Acyclovir	Vidarabine	Preclinical	Vero cell	PMID:6285731		x				
118	VZV	Acyclovir	Vidarabine	Preclinical	WI-38 cell	PMID:6285731		x				
119	VZV	Acyclovir	Vidarabine	Preclinical	MRC-5 cell	PMID:6285733	x	x				

120	CMV	Acyclovir	Zidovudine	Preclinical	HEL cell	PMID:1337893	x	x				
121	HBV	Adefovir	Clevudine	4	Human	NCT01263002						N/A
122	HBV	Adefovir	Emtricitabine	Preclinical	HepG2 cell	PMID:15388423		x				
123	HBV	Adefovir	Entecavir	Preclinical	HepG2 cell	PMID:15388423	x					
124	HBV	Adefovir	Entecavir	4	Human	PMID:23650172;NCT01023217					x	
125	HBV	Adefovir	Interferon Alpha	4	Human	NCT00922207						N/A
126	HBV	Adefovir	Lamivudine	Preclinical	Huh-7 cell	PMID:10681317	x	x				
127	HBV	Adefovir	Lamivudine	Preclinical	HepG2 cell	PMID:15388423		x				
128	HBV	Adefovir	Lamivudine	4	Human	PMID:23650173;NCT01023217						x
129	HBV	Adefovir	Penciclovir	Preclinical	Huh-7 cell	PMID:10681317	x	x				
130	HBV	Adefovir	Telbivudine	Preclinical	HepG2 cell	PMID:15388423		x				
131	HBV	Adefovir	Tenofovir	Preclinical	HepG2 cell	PMID:15388423	x					
132	HBV	Adefovir	Tenofovir	Preclinical	AD38 cell	PMID:19374144		x				
133	HIV	Adefovir	Zidovudine	1	Human	NCT00002326						N/A
134	RVFV	Adezmapimod	Rapamycin	Preclinical	H2.36 cell	PMID:29652799	x					
135	TGEV	AG1024	Ouabain	Preclinical	ST cell	PMID:35215353		x				
136	EV-A71	ALD	NK-1.9K	Preclinical	RD;Vero;HEK293T cell	PMID:28063993	x					
137	HIV	Aldesleukin	Zidovudine	1	Human	NCT00001005						N/A
138	HCV	Alfosbuvir	Daclatasvir	2	Human	PMID:35080256,NCT04070235					x	
139	HCV	Alisporivir	Boceprevir	Preclinical	Huh-7 cell	PMID:24687498		x				
140	HCV	Alisporivir	Daclatasvir	Preclinical	Huh-7 cell	PMID:24687498	x					
141	HCV	Alisporivir	Dasatinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
142	HCV	Alisporivir	Erlotinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
143	HCV	Alisporivir	Mericitabine	Preclinical	Huh-7 cell	PMID:24687498	x					
144	HCV	Alisporivir	Ribavirin	2	Human	PMID:26118427,NCT02094443					x	
145	MERS-CoV	Alisporivir	Ribavirin	Preclinical	LLC-MK2 cell	PMID:27840112		x				
146	SARS-CoV	Alisporivir	Ribavirin	Preclinical	Mice	PMID:27840112				x		
147	HCV	Alisporivir	Sofosbuvir	Preclinical	Huh-7 cell	PMID:24687498	x					
148	HCV	Alisporivir	Telaprevir	Preclinical	Huh-7 cell	PMID:24687498	x					
149	HBV	Alisporivir	Telbivudine	Preclinical	HepG2.2.15 cell	PMID:25305505					x	
150	RSV	Alivizumab	Ribavirin	0/1	Human	PMID:18043443					x	
151	FLUAV	Alpha-Tocopherol	Oseltamivir	Preclinical	Mice	PMID:27341844					x	
152	HIV	Alvircept Sudotox	Zidovudine	1	Human	NCT00000743						N/A
153	FLUAV	Amantadine	Arbidol	Preclinical	Unknown	PMID:16206613					x	
154	FLUAV	Amantadine	Diphyllin	Preclinical	MDCK cell	PMID:23820269					x	
155	HCV	Amantadine	Interferon Alpha	0/1	Human	PMID:16984502				x		
156	FLUAV	Amantadine	Oseltamivir	Preclinical	Mice	PMID:17591026					x	
157	FLUAV	Amantadine	Oseltamivir	Preclinical	MDCK cell	PMID:19273672	x					
158	FLUAV	Amantadine	Ribavirin	Preclinical	MDCK cell	PMID:19273672	x					
159	FLUAV	Amantadine	Ribavirin	Preclinical	Mice	PMID:7396454					x	
160	FLUBV	Amantadine	Ribavirin	Preclinical	Mice	PMID:7396454					x	
161	HIV	Amdoxovir	Zidovudine	2	Human	PMID:20386073;NCT00432016	x					
162	VZV	Amenamevir	Penciclovir	Preclinical	MRC-5 cell	PMID:23261844	x					
163	HSV-2	Amenamevir	Penciclovir	Preclinical	Vero cell	PMID:23261844	x					
164	VZV	Amenamevir	Vidarabine	Preclinical	MRC-5 cell	PMID:23261844	x					
165	HSV-2	Amenamevir	Vidarabine	Preclinical	Vero cell	PMID:23261844		x				
166	CHIKV	AmiRNA	AmiRNA	Preclinical	Vero cell	PMID:27565991					x	
167	CHIKV	AmiRNA	Chloroquine	Preclinical	Vero cell	PMID:27565991					x	
168	HAdV	AmiRNA	Cidofovir	Preclinical	A549 cell	PMID:23127366		x				
169	CHIKV	AmiRNA	Mycophenolic Acid	Preclinical	Vero cell	PMID:27565991			x			
170	CHIKV	AmiRNA	Ribavirin	Preclinical	Vero cell	PMID:27565991			x			
171	WNV	Ammonium Trichloro(Dioxyethylene-0-0')Tellurate (AS101)	Antibodies	Preclinical	Mice	PMID:22445690		x				
172	EBOV	Amodiaquine	Artesunate	0/1	Human	PMID:26735991					x	
173	SARS-CoV-2	Amodiaquine	Artesunate	Preclinical	Vero cell	PMID:32805422						x
174	SARS-CoV-2	Amodiaquine	Lopinavir	Preclinical	Vero cell	PMID:33333292	x					
175	SARS-CoV-2	Amodiaquine	Nitazoxanide	Preclinical	Vero cell	PMID:33333292	x					
176	SARS-CoV-2	Amodiaquine	Remdesivir	Preclinical	Vero cell	PMID:33333292	x		x			
177	SARS-CoV-2	Amodiaquine	Umifenovir	Preclinical	Vero cell	PMID:33333292	x					
178	HIV-1	Amprenavir	Efavirenz	0/1	Human	PMID:10671334					x	
179	HIV-1	Amprenavir	Fosamprenavir	0/1	Human	PMID:15728914				x		
180	HIV-1	Amprenavir	Ritonavir	0/1	Human	PMID:15728914						x
181	FLUAV	Amylmetacresol	Dichlorobenzyl Alcohol	Preclinical	Unknown	PMID:15889535					x	
182	RSV	Amylmetacresol	Dichlorobenzyl Alcohol	Preclinical	Unknown	PMID:15889535					x	
183	SARS-CoV	Amylmetacresol	Dichlorobenzyl Alcohol	Preclinical	Unknown	PMID:15889535					x	
184	ECHOV-1	Anisomycin	Rupintrivir	Preclinical	A549 cell	PMID:36146673		x				
185	ECHOV-1	Anisomycin	Vemurafenib	Preclinical	A549 cell	PMID:33080984	x					
186	SARS-CoV-2	Antibodies	Antibodies	0/1	Human	ChiCTR2000030580						N/A
187	SARS-CoV-2	Antibodies	Antibodies	2	Human	NCT04787211						N/A
188	SARS-CoV-2	Antibodies	Antibodies	4	Human	NCT05502081						N/A
189	VACV	Antibodies	Antibodies	Preclinical	Mice	PMID:16227266					x	
190	SARS-CoV	Antibodies	Antibodies	Preclinical	FRhK-4 cell	PMID:16796401	x					
191	VACV	Antibodies	Antibodies	Preclinical	Mice	PMID:20587859					x	
192	CHIKV	Antibodies	Antibodies	Preclinical	Mice	PMID:23125446					x	
193	PV	Antibodies	Antibodies	Preclinical	Unknown	PMID:24824031					x	
194	CHIKV	Antibodies	Antibodies	Preclinical	Mice	PMID:28148840					x	
195	SARS-CoV-2	Antibodies	Antibodies	3	Human	PMID:35443106,NCT04625725					x	
196	SARS-CoV-2	Antibodies	Antibodies	Preclinical	Mice	PMID:35060840	x					
197	FLUAV	Antibodies	Antibodies	Preclinical	Mice	PMID:35240918					x	
198	HIV-1	Antibodies	Antibodies	1	Human	PMID:35418681					x	
199	SARS-CoV-2	Antibodies	Antibodies	N/A	Human	PMID:35727429					x	
200	SARS-CoV-2	Antibodies	Antibodies	Preclinical	Hamster	PMID:36189212					x	

201	SARS-CoV-2	Antibodies	Antibodies	Preclinical	Vero E6 cell	PMID:36189212					x		
202	JCV	Antibodies	Chlorpromazine	Preclinical	SVG cell	PMID:11517408	x						
203	VACV	Antibodies	Cidofovir	Preclinical	Mice	PMID:25385098					x		
204	HSV-1	Antibodies	Foscarnet	Preclinical	Vero cell	PMID:29357297	x						
205	HSV-2	Antibodies	Foscarnet	Preclinical	Vero cell	PMID:29357297	x						
206	HIV-1	Antibodies	Fostemsavir	Preclinical	Unknown	PMID:30518644	x						
207	CMV	Antibodies	Ganciclovir	0/1	Human	NCT00001999							N/A
208	HSV-1	Antibodies	Ganciclovir	Preclinical	Vero cell	PMID:29357297	x						
209	HSV-2	Antibodies	Ganciclovir	Preclinical	Vero cell	PMID:29357297	x		x				
210	MERS-CoV	Antibodies	HR2P-M2	Preclinical	293T;Huh-7 cell	PMID:30621343	x						
211	SARS-CoV-2	Antibodies	Hydroxychloroquine	4	Human	PMID:34764044					x		
212	EBOV	Antibodies	Interferon	Preclinical	Guinea Pig	PMID:23616649					x		
213	PV-1	Antibodies	Interferon Alpha	Preclinical	Unknown	PMID:1665535	x	x					
214	SINV	Antibodies	Interferon Alpha	Preclinical	AT-3 cell	PMID:7474167	x						
215	CV-A214	Antibodies	Interferon Beta	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
216	HAdV	Antibodies	Interferon Beta	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
217	HDV	Antibodies	Interferon Beta	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
218	HSV-1	Antibodies	Interferon Beta	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
219	SINV	Antibodies	Interferon Gamma	Preclinical	Mice	PMID:17376910					x		
220	CV-A214	Antibodies	Interferon Gamma	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
221	HAdV	Antibodies	Interferon Gamma	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
222	HDV	Antibodies	Interferon Gamma	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
223	HSV-1	Antibodies	Interferon Gamma	Preclinical	WISH;RK-13 cell	PMID:6190753	x						
224	HIV-1	Antibodies	Maraviroc	Preclinical	Unknown	PMID:26354735	x						
225	HIV	Antibodies	Nevirapine	3	Human	PMID:21826009;NCT00639938				x			
226	FLUAV	Antibodies	Oseltamivir	Preclinical	Ferret	PMID:28633457					x		
227	HSV-1	Antibodies	Penciclovir	Preclinical	Vero cell	PMID:29357297	x						
228	HSV-2	Antibodies	Penciclovir	Preclinical	Vero cell	PMID:29357297	x						
229	PV-2	Antibodies	Pleconaril	0/1	Human	PMID:12692287					x		
230	SARS-CoV-2	Antibodies	Remdesivir	4	Human	PMID:34764044					x		
231	SARS-CoV-2	Antibodies	Remdesivir	N/A	Human	PMID:34780850					x		
232	SUDV	Antibodies	Remdesivir	Preclinical	Macaque	PMID:35413016					x		
233	HMPV	Antibodies	Ribavirin	0/1	Human	PMID:19344395					x		
234	RSV	Antibodies	Ribavirin	Preclinical	Cotton Rat	PMID:3550674					x		
235	LASV	Antibodies	Ribavirin	Preclinical	Cynomolgus Monkey	PMID:6715898					x		
236	HBV	Antibodies	SiRNA	Preclinical	HMF;Hela cell	PMID:19591879	x						
237	CVB-3	Antibodies	SiRNA	Preclinical	Hela cell	PMID:25193982		x					
238	CVB-3	Antibodies	SiRNA	Preclinical	Mice	PMID:25193982		x					
239	DENV	Antibodies	Sunitinib	Preclinical	Mice	PMID:30071205	x						
240	HIV-1	Antibodies	Vesatolimod	Preclinical	Macaque	PMID:35452496					x		
241	HBV	Antigen	Interleukin-12	1	Human	NCT02431312							N/A
242	HSV-1	Aphidicolin	Cidofovir	Preclinical	Vero cell	PMID:12087926	x						
243	EBOV	Apilimod	Azithromycin	Preclinical	Huh-7 cell	PMID:29939303	x						
244	EBOV	Apilimod	Clomiphene	Preclinical	Huh-7 cell	PMID:29939303	x						
245	EBOV	Apilimod	Toremifene	Preclinical	Huh-7 cell	PMID:29939303	x						
246	FLUAV	Aprotinin	AV5080	Preclinical	Mice	PMID:35956925					x		
247	FLUAV	Aprotinin	Favipiravir	Preclinical	Mice	PMID:35956925					x		
248	SARS-CoV-2	Aprotinin	Favipiravir	Preclinical	Mice	PMID:35956925				x			
249	FLUAV	Aprotinin	Molnupiravir	Preclinical	Mice	PMID:35956925					x		
250	SARS-CoV-2	Aprotinin	Molnupiravir	Preclinical	Mice	PMID:35956925					x		
251	SARS-CoV-2	Aprotinin	Nirmatrelvir	Preclinical	Mice	PMID:35956925					x		
252	FLUAV	Aprotinin	Remdesivir	Preclinical	Mice	PMID:35956925					x		
253	SARS-CoV-2	Aprotinin	Remdesivir	Preclinical	Mice	PMID:35956925				x			
254	FLUAV	Aprotinin	Rimantadine	Preclinical	Mice	PMID:2434613	x						
255	SARS-CoV-2	Arbidol	Interferon Alpha	0/1	Human	NCT04273763							N/A
256	SARS-CoV-2	Arbidol	Novaferon	0/1	Human	ChiCTR2000029573							N/A
257	FLUAV	Arbidol	Ribamidil	Preclinical	Unknown	PMID:16206613					x		
258	FLUAV	Arbidol	Ribavirin	Preclinical	Unknown	PMID:16206613					x		
259	FLUAV	Arbidol	Rimantadine	Preclinical	Unknown	PMID:16206613					x		
260	HBV	ARC-520	Tenofovir	2	Human	NCT02452528							N/A
261	PV-1	Arildone	Disoxaril	Preclinical	FL cell	PMID:10757231			x				
262	PV-1	Arildone	Enviroxime	Preclinical	FL cell	PMID:10757231	x	x					
263	PV-1	Arildone	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Preclinical	FL cell	PMID:10757231			x				
264	PV-1	Arildone	Guanidine	Preclinical	FL cell	PMID:10757231			x				
265	PV-1	Arildone	N-Phenyl-N′-3-Hydroxyphenylthiourea(PTU-23)	Preclinical	FL cell	PMID:10757231	x						
266	CVB-1	Arildone	N-Phenyl-N′-3-Hydroxyphenylthiourea(PTU-23)	Preclinical	Cell culture	PMID:15026197	x						
267	EBOV	Aripiprazole	Piperacetazine	Preclinical	Huh-7 cell	PMID:29939303	x						
268	SARS-CoV-2	Artemether	Lumefantrine	Preclinical	Vero cell	PMID:32805422							x
269	SARS-CoV-2	Artemether	Lumefantrine	Preclinical	Vero E6 cell	PMID:32805422							x
270	SARS-CoV-2	Artemether	Pyronaridine	Preclinical	Vero cell	PMID:32805422							x
271	SARS-CoV-2	Artenimol	Piperaquine	Preclinical	Vero cell	PMID:32805422							x
272	SARS-CoV-2	Artenimol	Piperaquine	Preclinical	Vero E6 cell	PMID:32805422							x
273	CMV	Artesunate	Cidofovir	Preclinical	MRC-5 cell	PMID:26844400	x						
274	CMV	Artesunate	Foscarnet	Preclinical	MRC-5 cell	PMID:26844400	x						
275	CMV	Artesunate	Ganciclovir	Preclinical	MRC-5 cell	PMID:26844400	x						
276	CMV	Artesunate	Letermovir	Preclinical	MRC-5 cell	PMID:26844400	x						
277	CMV	Artesunate	Maribavir	Preclinical	MRC-5 cell	PMID:26844400	x						
278	SARS-CoV-2	Artesunate	Mefloquine	Preclinical	Vero cell	PMID:32805422							x
279	SARS-CoV-2	Artesunate	Pyronaridine	Preclinical	Vero cell	PMID:32805422							x
280	CMV	Artesunate	Sunitinib	Preclinical	HFF cell	PMID:24277030	x						

281	HIV-1	Artesunate	Valacyclovir	Preclinical	Mice	PMID:26374952					x		
282	SARS-CoV-2	ASC09	Ritonavir	0/1	Human	NCT04261907							N/A
283	HCV	Asunaprevir	Daclatasvir	2	Human	PMID:26683763;NCT01012895							x
284	HCV	Asunaprevir	Interferon Lambda	Preclinical	Huh-7 cell	PMID:23274666	x	x					
285	HIV	Atazanavir	Raltegravir	3	Human	NCT00874523							N/A
286	HIV	Atazanavir	Ritonavir	4	Human	NCT00384904							N/A
287	SARS-CoV-2	Atazanavir	Ritonavir	Preclinical	Vero cell	PMID:32759267					x		
288	HIV	Atevirdine	Zidovudine	2	Human	NCT00002322							N/A
289	SARS-CoV-2	Atglistatin	Oseltamivir	Preclinical	Hamster	PMID:36253361	x						
290	SARS-CoV-2	Atglistatin	Remdesivir	Preclinical	Hamster	PMID:36253361	x						
291	FLUAV	Atomoxetine	Oseltamivir	Preclinical	MDCK cell	PMID:35238349			x				
292	HBV	Atorvastatin	Tenofovir	N/A	Human	PMID:35873362					x		
293	SARS-CoV-2	Avoralstat	Molnupiravir	Preclinical	293TAT cell	PMID:36190406	x						
294	SARS-CoV-2	Avoralstat	Molnupiravir	Preclinical	Calu-3 cell	PMID:36190406		x					
295	HIV-1	Azacitidine	Clofarabine	Preclinical	U373-MAGI cell	PMID:27117260	x						
296	HIV-1	Azacitidine	Gemcitabine	Preclinical	U373-MAGI cell	PMID:27117260	x						
297	HIV-1	Azacitidine	Hydroxyurea	Preclinical	U373-MAGI cell	PMID:27117260	x						
298	HIV-1	Azacitidine	Resveratrol	Preclinical	U373-MAGI cell	PMID:27117260	x						
299	FLUAV	AZD-8330	Oseltamivir	Preclinical	A549 cell	PMID:23523553	x						
300	SARS-CoV-2	Azithromycin	Chloroquine	0/1	Human	PMID:35227869					x		
301	EBOV	Azithromycin	Digitoxin	Preclinical	HEK293 cell	PMID:31806372		x					
302	EBOV	Azithromycin	Fluvastatin	Preclinical	HEK293 cell	PMID:31806372	x						
303	SARS-CoV-2	Azithromycin	Hydroxychloroquine	3	Human	PMID:32205204;DOI:10.1016/j.ijantimicag.2020.105949					x		
304	FLUAV	Azithromycin	Oseltamivir	2	Human	PMID:24632748;UMIN000005371				x			
305	FLUAV	Baloxavir Marboxil	Favipiravir	Preclinical	MDCK cell	PMID:33049959	x						
306	FLUAV	Baloxavir Marboxil	Oseltamivir	Preclinical	Mice	PMID:30476172	x						
307	FLUAV	Baloxavir Marboxil	Oseltamivir	Preclinical	MDCK cell	PMID:33049959	x						
308	FLUAV	Baloxavir Marboxil	Oseltamivir	1	Human	PMID:34756990					x		
309	FLUAV	Baloxavir Marboxil	Oseltamivir	Preclinical	MDCK;A549 cell	PMID:35062315	x						
310	FLUAV	Baloxavir Marboxil	Oseltamivir	Preclinical	Ferret	PMID:35938724				x			
311	FLUAV	Baloxavir Marboxil	Peramivir	Preclinical	MDCK cell	PMID:33049959	x						
312	FLUAV	Baloxavir Marboxil	Peramivir	Preclinical	MDCK;A549 cell	PMID:35062315	x						
313	FLUAV	Baloxavir Marboxil	Ribavirin	Preclinical	MDCK cell	PMID:33049959			x				
314	FLUAV	Baloxavir Marboxil	Zanamivir	Preclinical	MDCK cell	PMID:33049959	x						
315	SARS-CoV-2	Baricitinib	Remdesivir	N/A	Human	PMID:35443520					x		
316	SARS-CoV-2	Baricitinib	Remdesivir	Preclinical	HLE-ALI cell	PMID:35688145					x		
317	HCV	Bavituximab	Ribavirin	2	Human	NCT01273948							N/A
318	CMV	BDCRB	Maribavir	Preclinical	MRC-5 cell	PMID:12323400	x						
319	CMV	BDCRB	Tomeglovir	Preclinical	MRC-5 cell	PMID:12323400	x		x				
320	HCV	Beclabuvir	Interferon Lambda	Preclinical	Huh-7 cell	PMID:23274666		x					
321	EBOV	Bepridil	Sertraline	Preclinical	Huh-7 cell	PMID:29939303	x						
322	EBOV	Bepridil	Sertraline	Preclinical	Mice	PMID:33801811;PMID:29939303							x
323	RVFV	BI-D1870	PF-4708671	Preclinical	H2.35 cell	PMID:29652799					x		
324	HIV-1	BMS-663068	Ritonavir	2	Human	PMID:26902761;NCT01009814							x
325	HCV	Boceprevir	Daclatasvir	Preclinical	Huh-7 cell	PMID:27035622	x	x	x				
326	HCV	Boceprevir	Dasatinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x						
327	HCV	Boceprevir	Erlotinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x						
328	HCV	Boceprevir	Sofosbuvir	Preclinical	Huh-7 cell	PMID:27035622		x	x				
329	HCV	Boceprevir	Telaprevir	Preclinical	Huh-7 cell	PMID:27035622		x	x				
330	SARS-CoV-2	Brequinar	Dipyridamole	Preclinical	A549/ACE2; HEK293T-hACE2 cell	PMID:36041646	x						
331	HIV-1	Brequinar	Lamivudine	Preclinical	TZM-bl cell	PMID:33080984							x
332	SARS-CoV-2	Brequinar	Molnupiravir	Preclinical	Calu-3 cell	PMID:36190406	x						
333	SARS-CoV-2	Brequinar	N4-Hydroxycytidine	Preclinical	Vero E6 cell	PMID:35492218	x						
334	HCV	Brequinar	Sofosbuvir	Preclinical	Huh-7.5 cell	PMID:33080984	x						
335	HIV-1	Brequinar	Tenofovir	Preclinical	TZM-bl cell	PMID:33080984							x
336	CMV	Brincidofovir	Letermovir	Preclinical	HFF cell	PMID:30153445	x						
337	CPXV	Brincidofovir	Tecovirimat	Preclinical	HFF cell	PMID:17724153	x						
338	VACV	Brincidofovir	Tecovirimat	Preclinical	HFF cell	PMID:17724153	x						
339	CPXV	Brincidofovir	Tecovirimat	Preclinical	Mice	PMID:17724153	x						
340	HAdV	Brincidofovir	Valganciclovir	Preclinical	Hamster	PMID:28827083					x		
341	HSV-1	Brivudine	Foscarnet	Preclinical	Vero cell	PMID:6285731	x						
342	HSV-2	Brivudine	Foscarnet	Preclinical	Vero cell	PMID:6285731		x					
343	VZV	Brivudine	Interferon Alpha	Preclinical	HuEF cell	PMID:6329083	x	x					
344	HSV-1	Brivudine	Vidarabine	Preclinical	Vero cell	PMID:6285731		x					
345	HSV-2	Brivudine	Vidarabine	Preclinical	Vero cell	PMID:6285731	x						
346	VACV	Broxuridine	Noformicin	Preclinical	Unknown	PMID:14231461					x		
347	HIV	Butyldeoxynojirimycin	Zidovudine	2	Human	PMID:7905523;NCT00001993							x
348	HIV-1	Cabotegravir	Lenacapavir	Preclinical	HEK293/17, TZM-gfp cell	PMID:35746673		x					
349	FLUAV	Caffeine	Lovastatin	Preclinical	Mice	PMID:19616097					x		
350	SARS-CoV-2	Camostat	Molnupiravir	Preclinical	293TAT cell	PMID:36190406	x						
351	SARS-CoV-2	Camostat	Molnupiravir	Preclinical	Calu-3 cell	PMID:36190406	x						
352	FLUAV	Camphecene	Oseltamivir	Preclinical	Mice	PMID:34984730		x					
353	MCV	Cantharidin	Imiquimod	0/1	Human	PMID:15068455					x		
354	VACV	Carbenoxolone	Prostaglandin A1	Preclinical	L929 cell	PMID:9477119	x						
355	HSV-1	Carbocyclic Oxetanocin G	Oxetanocin G	Preclinical	Vero cell	PMID:1333651	x						
356	HSV-2	Carbocyclic Oxetanocin G	Oxetanocin G	Preclinical	Vero cell	PMID:1333651		x					
357	FLUAV	Carrageenan	Zanamivir	Preclinical	MDCK cell	PMID:26053018	x						
358	SARS-CoV-2	Carvedilol	Favipiravir	Preclinical	3CL Protease assay kit	PMID:36110398	x						
359	LASV	Casticin	F1204	Preclinical	Vero cell	PMID:34965446	x						
360	LASV	Casticin	F1781	Preclinical	Vero cell	PMID:34965446	x						

361	SARS-CoV-2	Cefixime	Favipiravir	Preclinical	3CL Protease assay kit	PMID:36110398	x					
362	SARS-CoV-2	Cepharanthine	Nelfinavir	Preclinical	Vero E6 cell	PMID:33080984						x
363	HCV	Chlorcyclizine	Ribavirin	1	Human	PMID:30711416;NCT02118012	x					
364	HCV	Chlorcyclizine	Telaprevir	Preclinical	Huh-7.5.1;Con1b cell	PMID:27035622	x					
365	EBOV	Chloroquine	Fluvastatin	Preclinical	HEK293 cell	PMID:31806372	x					
366	SARS-CoV-2	Chloroquine	Ivermectin	Preclinical	Vero E6 cell	PMID:35717393		x				
367	SARS-CoV-2	Chloroquine	Niclosamide	Preclinical	Vero E6 cell	PMID:35717393	x	x				
368	SARS-CoV-2	Chloroquine	Oseltamivir	3	Human	NCT04303299						N/A
369	CCHFV	Chloroquine	Ribavirin	Preclinical	Vero cell	PMID:25796972	x					
370	EBOV	Chloroquine	Tetradrine	Preclinical	HEK293 cell	PMID:31806372	x					
371	CCHFV	Chlorpromazine	Ribavirin	Preclinical	Vero cell	PMID:25796972	x					
372	FLUAV	Chrysin	Nifurtimox	Preclinical	A549 cell	PMID:35216485	x					
373	EBOV	Cidofovir	Favipiravir	Preclinical	293T cell	PMID:26752302			x			
374	CMV	Cidofovir	Foscarnet	Preclinical	HEL cell	PMID:1337893	x	x				
375	HHV-6	Cidofovir	Foscarnet	0/1	Human	PMID:17516391					x	
376	CMV	Cidofovir	Ganciclovir	Preclinical	HEL cell	PMID:1337893	x	x				
377	VACV	Cidofovir	Idoxuridine	Preclinical	Cef cell	PMID:17042327	x					
378	EBOV	Cidofovir	Interferon Alpha	Preclinical	293T cell	PMID:26752302			x			
379	EBOV	Cidofovir	Interferon Beta	Preclinical	293T cell	PMID:26752302	x					
380	CMV	Cidofovir	Lactoferrin	Preclinical	Flf	PMID:12742576	x					
381	EBOV	Cidofovir	Lamivudine	Preclinical	293T cell	PMID:26752302	x					
382	CMV	Cidofovir	Letermovir	Preclinical	NHDF cell	PMID:25779572		x				
383	CMV	Cidofovir	Maribavir	Preclinical	MRC-5 cell	PMID:12323400	x					
384	CMV	Cidofovir	Maribavir	Preclinical	ARPEp cell	PMID:30040968		x				
385	VACV	Cidofovir	SiRNA	Preclinical	HEL cell	PMID:19307376	x					
386	EBOV	Cidofovir	Tenofovir	Preclinical	293T cell	PMID:26752302			x			
387	EBOV	Cidofovir	Toremifene	Preclinical	293T cell	PMID:26752302	x					
388	CMV	Cidofovir	Zidovudine	Preclinical	HEL cell	PMID:1337893	x	x				
389	EBOV	Cidofovir	Zidovudine	Preclinical	293T cell	PMID:26752302			x			
390	HBV	Clevudine	Interferon Alpha	4	Human	NCT01264367						N/A
391	HBV	Clevudine	Lamivudine	4	Human	NCT00798460						N/A
392	HBV	Clevudine	Tenofovir	3	Human	NCT00823342						N/A
393	EBOV	Clomiphene	Sertraline	Preclinical	Huh-7 cell	PMID:29939303	x					
394	HEV	CMLD012118	Interferon Alpha	Preclinical	HepG2 cell	PMID:35728703		x				
395	HEV	CMLD012118	Ribavirin	Preclinical	HepG2 cell	PMID:35728703		x				
396	HIV-1	Cobicistat	Darunavir	3	Human	NCT02987530						N/A
397	HIV-1	Cobicistat	Darunavir	1	Human	NCT05197075						N/A
398	SARS-CoV-2	Cobicistat	Darunavir	3	Human	PMID:32671131;NCT04252274				x		
399	HIV-1	Cobicistat	Darunavir	N/A	Human	PMID:35658217					x	
400	HIV-1	Cobicistat	GSK2838232	2	Human	PMID:31769793;NCT03045861					x	
401	SARS-CoV-2	Cobicistat	Remdesivir	Preclinical	Hamster	PMID:35229634					x	
402	SARS-CoV-2	Cobicistat	Remdesivir	Preclinical	T84 cell	PMID:35229634	x					
403	SARS-CoV-2	Cobicistat	Remdesivir	Preclinical	Vero E6 cell	PMID:35229634	x					
404	HCV	Coblopasvir	Sofosbuvir	3	Human	NCT03995485						N/A
405	TBEV	Cycloheximide	Dactinomycin	Preclinical	Pig embryo kidney cell	PMID:6636703					x	
406	SARS-CoV-2	Cycloheximide	Nelfinavir	Preclinical	Vero E6 cell	PMID:33080984						x
407	ECHOV-1	Cycloheximide	Rupintrivir	Preclinical	A549 cell	PMID:36146673	x					
408	ECHOV-1	Cycloheximide	Vemurafenib	Preclinical	A549 cell	PMID:33080984	x					
409	B19V	Cyclosporine	HDIG	0/1	Human	PMID:15540900					x	
410	HCV	Cyclosporine	Interferon Alpha	Preclinical	Huh-7 cell	PMID:17101321	x					
411	MERS-CoV	Cyclosporine	Interferon Alpha	Preclinical	Human lung microvascular endothelial cell	PMID:29772254					x	
412	CMV	Cyclosporine	Mycophenolic Acid	4	Human	NCT02328963,PMID:34725108					x	
413	HCV	Cyclosporine	Mycophenolic Acid	Preclinical	Huh-7 cell	PMID:17101321	x					
414	NoV	Cyclosporine	Mycophenolic Acid	Preclinical	HG23 Cell	PMID:28807916		x				
415	NoV	Cyclosporine	Ribavirin	Preclinical	HG23 Cell	PMID:28807916		x				
416	NoV	Cyclosporine	Tacrolimus	Preclinical	HG23 Cell	PMID:28807916	x					
417	HIV	Cysteamine	Zidovudine	2	Human	NCT00002110						N/A
418	SARS-CoV-2	D,L-Lysine-Acetylsalicylate+Glycine	Remdesivir	Preclinical	Calu-3 cell	PMID:35805887		x				
419	HCV	Daclatasvir	Dasatinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
420	HCV	Daclatasvir	Erlotinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
421	SARS-CoV-2	Daclatasvir	Favipiravir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x					
422	HCV	Daclatasvir	Interferon Lambda	Preclinical	Huh-7 cell	PMID:23274666	x	x				
423	HCV	Daclatasvir	INX-08189	2	Human	NCT01425970						N/A
424	SARS-CoV-2	Daclatasvir	Remdesivir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144		x				
425	HCV	Daclatasvir	Sanglifehrin B	Preclinical	Huh-7 cell	PMID:24687498	x	x				
426	HCV	Daclatasvir	Simeprevir	2	Human	PMID:26453968;NCT01628692					x	
427	HCV	Daclatasvir	Sofosbuvir	Preclinical	Huh-7 cell	PMID:27035622	x					
428	HCV	Daclatasvir	Sofosbuvir	4	Human	PMID:31504303;NCT03200184					x	
429	YFV	Daclatasvir	Sofosbuvir	Preclinical	Huh-7 cell	PMID:31594756					x	
430	SARS-CoV-2	Daclatasvir	Sofosbuvir	3	Human	PMID:34849957				x		
431	SARS-CoV-2	Daclatasvir	Sofosbuvir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x					
432	HCV	Daclatasvir	Telaprevir	Preclinical	Huh-7 cell	PMID:27035622		x	x			
433	SARS-CoV-2	Daclatasvir	Tenofovir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x					
434	ECHOV-1	Dalbavancin	Rupintrivir	Preclinical	A549 cell	PMID:36146673		x				
435	FLUAV	Danirixin	Oseltamivir	2	Human	PMID:31024969;NCT02469298				x		
436	HCV	Danoprevir	Dasatinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
437	HCV	Danoprevir	Erlotinib	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
438	HCV	Danoprevir	Mericitabine	1	Human	PMID:20951424;NCT00801255					x	
439	SARS-CoV-2	Danoprevir	Ritonavir	4	Human	NCT04291729						N/A
440	HIV-1	Dapivirine	Tenofovir	Preclinical	TZM-bl cell	PMID:21633286	x					

441	HIV-1	Darunavir	Ritonavir		3	Human	PMID:23088336;NCT00258557					x	
442	CVB-3	Dasabuvir	PSI-6206	Preclinical		Hela cell	PMID:35789934	x					
443	HCV	Dasatinib	Erlotinib	Preclinical		Huh-7.5.1 cell	PMID:24848265	x					
444	HCV	Dasatinib	Mericitabine	Preclinical		Huh-7.5.1 cell	PMID:24848265	x					
445	HCV	Dasatinib	Simeprevir	Preclinical		Huh-7.5.1 cell	PMID:24848265	x					
446	HCV	Dasatinib	Sofosbuvir	Preclinical		Huh-7.5.1 cell	PMID:24848265	x					
447	HCV	Dasatinib	Telaprevir	Preclinical		Huh-7.5.1 cell	PMID:24848265	x					
448	HIV-1	Decitabine	Resveratrol	Preclinical		U373-MAGI cell	PMID:27117260	x					
449	HCV	Deleobuvir	Ravidasvir		2	Human	NCT01859962						N/A
450	FLUAV	Dextromethorphan	Oseltamivir	Preclinical		Mice	PMID:35238349					x	
451	HIV	Didanosine	Hydroxyurea		1	Human	PMID:15597521;NCT00001074					x	
452	HIV	Didanosine	Lentinan		1	Human	PMID:8721897;NCT00002098					x	
453	HIV	Didanosine	PEG IL-2	0/1		Human	NCT00001997						N/A
454	HIV	Didanosine	Ribavirin		1	Human	NCT00000833						N/A
455	HIV	Didanosine	Stavudine	0/1		Human	PMID:10449279;NCT00002207					x	
456	HIV	Didanosine	Timunox		3	Human	NCT00002109						N/A
457	HIV	Didanosine	Zidovudine		3	Human	NCT00001022						N/A
458	HIV-1	Didanosine	Zidovudine		2	Human	PMID:7727768					x	
459	CMV	Didox	Ganciclovir	Preclinical		MRC-5 cell	PMID:23933116	x					
460	EBOV	Digitoxin	Fluvastatin	Preclinical		HEK293 cell	PMID:31806372	x					
461	CMV	Digitoxin	Ganciclovir	Preclinical		HFF cell	PMID:24277030		x				
462	EBOV	Digitoxin	Tamoxifen	Preclinical		HEK293 cell	PMID:31806372	x					
463	EBOV	Digitoxin	Tetradrine	Preclinical		HEK293 cell	PMID:31806372	x					
464	CMV	Digoxin	Ganciclovir	Preclinical		HFF cell	PMID:24277030		x				
465	ECHOV-1	Digoxin	Rupintrivir	Preclinical		A549 cell	PMID:36146673			x			
466	HSV-1	Dinoprostone	Indomethacin	Preclinical		Raji;Raji-HSV cell	PMID:1964373				x		
467	HSV-1	Dinoprostone	Interferon Alpha	Preclinical		Raji;Raji-HSV cell	PMID:1964373				x		
468	FLUAV	Diphyllin	Oseltamivir	Preclinical		MDCK cell	PMID:23820269					x	
469	FLUAV	Dipyridamole	MEDS433	Preclinical		A549 cell	PMID:36298835	x					
470	PV-1	Disoxaril	Enviroxime	Preclinical		FL cell	PMID:10757231	x					
471	PV-1	Disoxaril	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Preclinical		FL cell	PMID:10757231			x			
472	PV-1	Disoxaril	Guanidine	Preclinical		FL cell	PMID:10757231			x			
473	PV-1	Disoxaril	N-Phenyl-N'-3-Hydroxyphenylthiourea(PTU-23)	Preclinical		FL cell	PMID:10757231	x					
474	CVB-1	Disoxaril	N-Phenyl-N'-3-Hydroxyphenylthiourea(PTU-23)	Preclinical		Cell culture	PMID:15026197	x					
475	HSV-1	Docosanol	Foscarnet	Preclinical		Vero cell	PMID:12367721		x				
476	HSV-1	Docosanol	Ribavirin	Preclinical		Vero cell	PMID:12367721	x					
477	HSV-1	Docosanol	Trifluridine	Preclinical		Vero cell	PMID:12367721	x					
478	HSV-1	Docosanol	Vidarabine	Preclinical		Vero cell	PMID:12367721	x					
479	HIV-1	Dolutegravir	Lamivudine		4	Human	NCT02211482,PMID:28537061					x	
480	HIV-1	Dolutegravir	Lamivudine	Preclinical		MT4-GFP cell	PMID:35491829				x		
481	HIV-1	Dolutegravir	Rilpivirine		3	Human	PMID:31307948;NCT02422797					x	
482	SARS-CoV-2	Doramapimod	Remdesivir	Preclinical		MRC5-ACE2 cell	PMID:34871905	x					
483	HIV	Doravirine	Emtricitabine		2	Human	PMID:31121013;NCT01632345						x
484	HIV-1	Doravirine	Islatravir		2	Human	NCT03272347						N/A
485	HIV-1	Doravirine	Islatravir	Preclinical		MT4-GFP cell	PMID:35491829	x					
486	HIV-1	Doravirine	Lamivudine	Preclinical		MT4-GFP cell	PMID:35491829				x		
487	KSHV	Doxorubicin	Rituximab		2	Human	PMID:25331113					x	
488	CHIKV	Doxycycline	Ribavirin	Preclinical		Mice	PMID:25970853					x	
489	CHIKV	Doxycycline	Ribavirin	Preclinical		Vero cell	PMID:25970853					x	
490	HSV-1	Edoxudine	Quercetin	Preclinical		Unknown	PMID:6151353	x					
491	HIV-1	Efavirenz	Indinavir	0/1		Human	NCT00002387						N/A
492	SARS-CoV-2	Efavirenz	Zidovudine	Preclinical		HEK293 cell	PMID:34755435	x					
493	CHIKV	EGCG	Suramin	Preclinical		U2Os cell	PMID:28760340	x					
494	HCV	Elbasvir	Grazoprevir		4	Human	PMID:31765046;NCT03111108					x	
495	SARS-CoV-2	Emetine	Nitazoxanide	Preclinical		Vero cell	PMID:33333292	x					
496	FLUAV	Emetine	Obatoclax	Preclinical		RPE cell	PMID:31635418						x
497	ECHOV-1	Emetine	Rupintrivir	Preclinical		A549 cell	PMID:36146673		x				
498	HCV	Emetine	Sofosbuvir	Preclinical		Huh-7.5 cell	PMID:33080984						x
499	ECHOV-1	Emetine	Vemurafenib	Preclinical		A549 cell	PMID:33080984	x					
500	ZIKV	Emricasan	Niclosamide	Preclinical		Human Astrocytes	PMID:27571349					x	
501	ZIKV	Emricasan	PHA-690509	Preclinical		Unknown	PMID:27571349		x				
502	HIV-1	Emtricitabine	Tenofovir		4	Human	NCT00362687						N/A
503	HBV	Emtricitabine	Tenofovir	Preclinical		AD38 cell	PMID:19374144	x	x				
504	HBV	Emtricitabine	Tenofovir		2	Human	PMID:21254162;NCT00298363						x
505	HIV-1	Emtricitabine	Tenofovir		3	Human	PMID:32711800						x
506	HIV-1	Emtricitabine	Tenofovir		1	Human	PMID:34878438						x
507	HIV-1	Enfuvirtide	Valproic Acid		1	Human	NCT00312546						N/A
508	HBV	Entecavir	Interferon Alpha		4	Human	NCT02360592						N/A
509	HBV	Entecavir	Resveratrol		2	Human	NCT03509688						N/A
510	HBV	Entecavir	Simvastatin		1	Human	NCT00994773						N/A
511	HBV	Entecavir	Tacrolimus		4	Human	PMID:35672893,NCT03062813					x	
512	HBV	Entecavir	Tenofovir		4	Human	NCT01639066,PMID:25800784				x		
513	HBV	Entecavir	Tenofovir	Preclinical		AD38 cell	PMID:19374144		x				
514	HBV	Entecavir	Thymosin A1		4	Human	NCT01938820						N/A
515	HCV	Entecavir	Vebicorvir		2	Human	PMID:35697332					x	
516	PV-1	Enviroxime	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Preclinical		FL cell	PMID:10757231	x					
517	CVB-1	Enviroxime	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Preclinical		Cell culture	PMID:15026197	x					
518	PV-1	Enviroxime	Guanidine	Preclinical		FL cell	PMID:10757231	x	x				
519	HRV-A2	Enviroxime	Interferon Gamma	Preclinical		WISH cell	PMID:3017203	x					
520	CVB-1	Enviroxime	N-Phenyl-N'-3-Hydroxyphenylthiourea(PTU-23)	Preclinical		Cell culture	PMID:15026197	x					

521	PV-1	Enviroxime	Ribavirin	Preclinical	Unknown	PMID:21466823	x		x			
522	EV-A71	Enviroxime	Rupintrivir	Preclinical	Unknown	PMID:21466823	x		x			
523	HRV-B14	Enviroxime	Rupintrivir	Preclinical	Unknown	PMID:21466823	x		x			
524	PV-1	Enviroxime	Rupintrivir	Preclinical	Unknown	PMID:21466823	x		x			
525	EV-A71	Enviroxime	Vapendavir	Preclinical	Unknown	PMID:21466823	x		x			
526	HRV-B14	Enviroxime	Vapendavir	Preclinical	Unknown	PMID:21466823	x	x				
527	PV-1	Enviroxime	Vapendavir	Preclinical	Unknown	PMID:21466823	x		x			
528	HCV	Erlotinib	Mericitabine	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
529	HCV	Erlotinib	Simeprevir	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
530	HCV	Erlotinib	Sofosbuvir	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
531	SARS-CoV-2	Erlotinib	Sunitinib	Preclinical	Calu-3 cell	PMID:35738348	x					
532	HCV	Erlotinib	Telaprevir	Preclinical	Huh-7.5.1 cell	PMID:24848265	x					
533	HSV-1	Etanercept	Valacyclovir	Preclinical	Mice	PMID:24416771					x	
534	PV-1	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	Guanidine	Preclinical	FL cell	PMID:10757231	x		x			
535	PV-1	Ethyl 4-Methyl-2-(Methylthio)Pyrimidine-5-Carboxylate	N-Phenyl-N′-3-Hydroxyphenylthiourea(PTU-23)	Preclinical	FL cell	PMID:10757231	x		x			
536	FLUAV	Eucalyptol	Oseltamivir	Preclinical	Mice	PMID:27966790	x					
537	BKV	Everolimus	Leflunomide	0/1	Human	PMID:28247521					x	
538	HIV-1	Ezetimibe	Lamivudine	Preclinical	TZM-bl cell	PMID:33080984						x
539	HIV-1	Ezetimibe	Tenofovir	Preclinical	TZM-bl cell	PMID:33080984						x
540	HCV	Faldaprevir	TD-6450	2	Human	NCT02716428						N/A
541	HBV	Famciclovir	Lamivudine	2	Human	PMID:12195876;PMID:10915748						x
542	FLUAV	Famotidine	Oseltamivir	Preclinical	Mice	PMID:35283537					x	
543	SARS-CoV-2	Farudodstat	N4-Hydroxycytidine	Preclinical	Vero E6 cell	PMID:35492218	x					
544	EBOV	Favipiravir	Interferon Alpha	Preclinical	293T cell	PMID:26752302	x					
545	ZIKV	Favipiravir	Interferon Alpha	Preclinical	Vero cell	PMID:29109164					x	
546	CHIKV	Favipiravir	Interferon Alpha	Preclinical	HFF-1 cell	PMID:33540830				x		
547	CHIKV	Favipiravir	Interferon Alpha	Preclinical	HT-1080 cell	PMID:33540830					x	
548	CHIKV	Favipiravir	Interferon Alpha	Preclinical	SK-N-MC cell	PMID:33540830					x	
549	EBOV	Favipiravir	Interferon Beta	Preclinical	293T cell	PMID:26752302	x					
550	EV-A71	Favipiravir	Itraconazole	Preclinical	RD cell	PMID:27353263	x					
551	EBOV	Favipiravir	Lamivudine	Preclinical	293T cell	PMID:26752302	x					
552	EBOV	Favipiravir	Merimepodib	Preclinical	Vero cell	PMID:29126899					x	
553	SARS-CoV-2	Favipiravir	Minocycline	0/1	Human	PMID:34627706					x	
554	SARS-CoV-2	Favipiravir	Nitazoxanide	2	Human	PMID:35869526						x
555	SARS-CoV-2	Favipiravir	Ombitasvir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x					
556	FLUAV	Favipiravir	Oseltamivir	2	Human	NCT03394209						N/A
557	FLUAV	Favipiravir	Oseltamivir	Preclinical	MDCK cell	PMID:24311151	x	x				
558	FLUAV	Favipiravir	Peramivir	Preclinical	Mice	PMID:22429564	x					
559	FLUAV	Favipiravir	Peramivir	Preclinical	MDCK cell	PMID:24311151	x	x				
560	FLUAV	Favipiravir	Peramivir	Preclinical	Mice	PMID:24992479	x		x			
561	SARS-CoV-2	Favipiravir	Pibrentasvir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x					
562	FLUAV	Favipiravir	Pimodivir	Preclinical	MDCK cell	PMID:25547360	x					
563	SARS-CoV-2	Favipiravir	Quercetin	N/A	Human	PMID:34863994					x	
564	JUNV	Favipiravir	Remdesivir	Preclinical	293T;Vero 76 cell	PMID:35816544	x					
565	RVFV	Favipiravir	Ribavirin	Preclinical	Hamster	PMID:24486952					x	
566	CCHFV	Favipiravir	Ribavirin	Preclinical	Mice	PMID:24786461	x		x			
567	LASV	Favipiravir	Ribavirin	Preclinical	Mice	PMID:26531247					x	
568	JUNV	Favipiravir	Ribavirin	Preclinical	Guinea Pig	PMID:26711718	x					
569	ZIKV	Favipiravir	Ribavirin	Preclinical	Vero cell	PMID:29109164			x			
570	EBOV	Favipiravir	Ribavirin	Preclinical	Cynomolgus Macaque	PMID:32135218				x		
571	JUNV	Favipiravir	Ribavirin	Preclinical	293T;Vero 76 cell	PMID:35816544	x					
572	NoV	Favipiravir	Rupintrivir	Preclinical	HG23 Cell	PMID:24890597		x				
573	EV-A71	Favipiravir	Rupintrivir	Preclinical	RD cell	PMID:27353263	x					
574	EV-A71	Favipiravir	Suramin	Preclinical	RD cell	PMID:27353263	x					
575	EBOV	Favipiravir	Tenofovir	Preclinical	293T cell	PMID:26752302	x					
576	SARS-CoV-2	Favipiravir	Tocilizumab	4	Human	PMID:3337898;ChiCTR2000030894						N/A
577	EBOV	Favipiravir	Toremifene	Preclinical	293T cell	PMID:26752302	x					
578	FLUAV	Favipiravir	Zanamivir	Preclinical	MDCK cell	PMID:24311151	x	x				
579	EBOV	Favipiravir	Zidovudine	Preclinical	293T cell	PMID:26752302	x					
580	FLUAV	Fenofibrate	Oseltamivir	Preclinical	Mice	PMID:25274854					x	
581	FLUAV	Fenofibrate	Simvastatin	Preclinical	Mice	PMID:25274854				x		
582	SARS-CoV-2	FK1706	Remdesivir	Preclinical	Vero E6 cell	PMID:35169800	x					
583	EBOV	Fluvastatin	Tamoxifen	Preclinical	HEK293 cell	PMID:31806372	x					
584	CMV	Fomivirsen	Ganciclovir	2	Human	NCT00002156						N/A
585	HIV-1	Fosamprenavir	Ritonavir	3	Human	NCT00144833						N/A
586	CMV	Foscarnet	Ganciclovir	3	Human	NCT00000136						N/A
587	CMV	Foscarnet	Ganciclovir	Preclinical	MRC-5 cell	PMID:12323400	x					
588	CMV	Foscarnet	Ganciclovir	Preclinical	HFF cell	PMID:24277030	x					
589	CMV	Foscarnet	Ganciclovir	Preclinical	Mice	PMID:2559657		x				
590	HSV-2	Foscarnet	Ganciclovir	Preclinical	Mice	PMID:2559657		x				
591	CMV	Foscarnet	Ganciclovir	Preclinical	MRC-5 cell	PMID:2559657	x					
592	HSV-2	Foscarnet	Ganciclovir	Preclinical	Vero cell	PMID:2559657	x					
593	CMV	Foscarnet	Lactoferrin	Preclinical	Flf	PMID:12742576			x			
594	CMV	Foscarnet	Leflunomide	0/1	Human	PMID:16688677					x	
595	CMV	Foscarnet	Letermovir	Preclinical	NHDF cell	PMID:25779572		x	x			
596	CMV	Foscarnet	Maribavir	Preclinical	MRC-5 cell	PMID:12323400	x					
597	CMV	Foscarnet	Maribavir	Preclinical	ARPEp cell	PMID:30040968		x				
598	HSV-1	Foscarnet	Vidarabine	Preclinical	Vero cell	PMID:6285731		x				
599	HSV-2	Foscarnet	Vidarabine	Preclinical	Vero cell	PMID:6285731		x				
600	CMV	Foscarnet	Zidovudine	Preclinical	HEL cell	PMID:1337893	x	x				

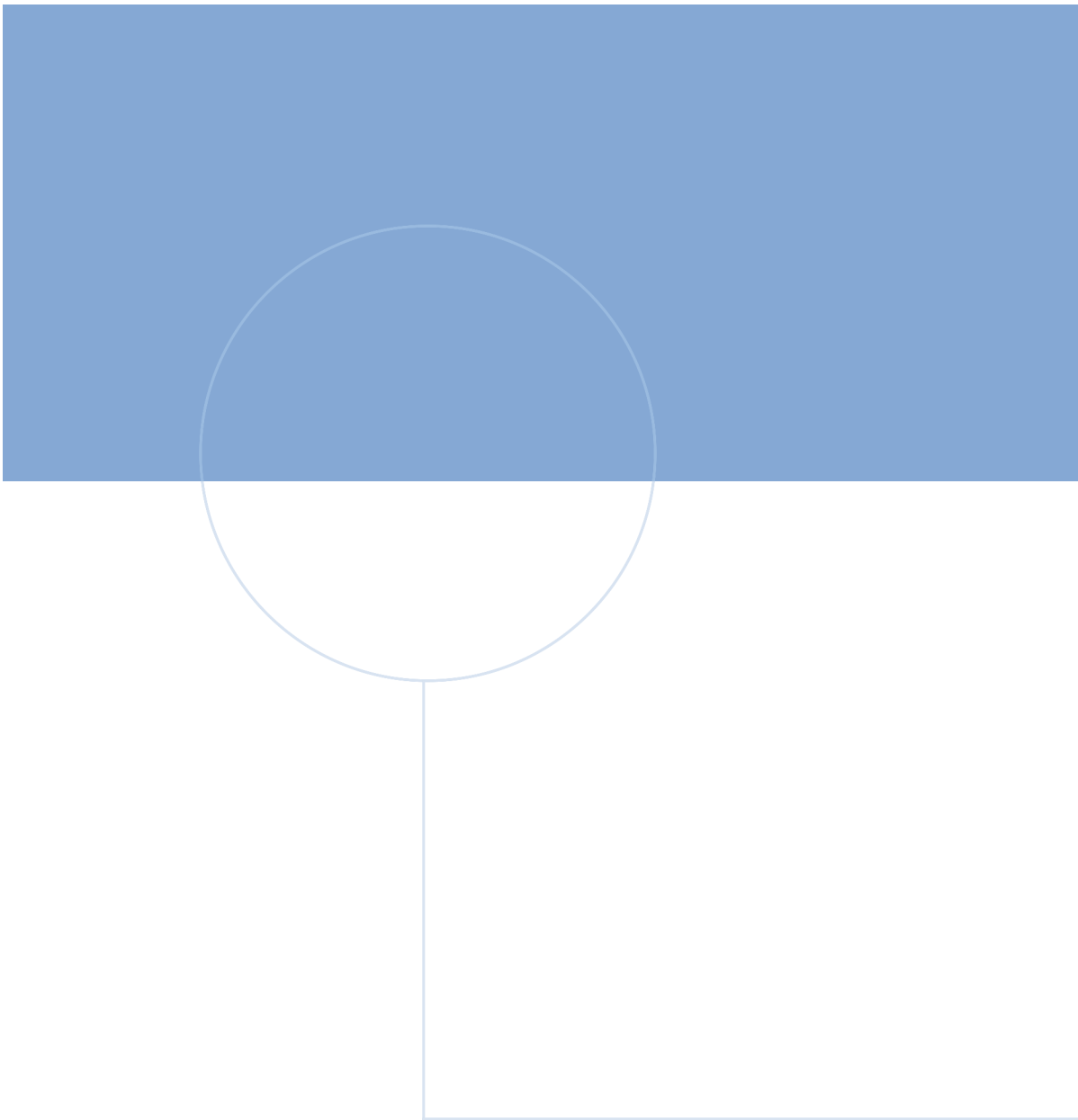
601	CMV	Ganciclovir	Hydroxyurea	Preclinical		MRC-5 cell	PMID:23933116	x					
602	HSV-1	Ganciclovir	Interferon Alpha	Preclinical		Unknown	PMID:2987369	x					
603	HSV-2	Ganciclovir	Interferon Alpha	Preclinical		Unknown	PMID:2987369	x					
604	CMV	Ganciclovir	ISIS 2922		2	Human	NCT00002156						N/A
605	CMV	Ganciclovir	Lactoferrin	Preclinical		Flf	PMID:12742576				x		
606	CMV	Ganciclovir	Letermovir	Preclinical		NHDF cell	PMID:25779572		x				
607	CMV	Ganciclovir	Maribavir	Preclinical		MRC-5 cell	PMID:12323400		x				
608	CMV	Ganciclovir	Maribavir	Preclinical		MRC-5 cell	PMID:26844400			x			
609	CMV	Ganciclovir	Maribavir	Preclinical		ARPEp cell	PMID:30040968			x			
610	CMV	Ganciclovir	Mizoribine	Preclinical		Unknown	PMID:20194528	x					
611	CMV	Ganciclovir	Ouabain	Preclinical		HFF cell	PMID:24277030		x				
612	CMV	Ganciclovir	Tomeglovir	Preclinical		MRC-5 cell	PMID:12323400			x			
613	CMV	Ganciclovir	Trimidox	Preclinical		MRC-5 cell	PMID:23933116	x					
614	CMV	Ganciclovir	Zidovudine	Preclinical		HEL cell	PMID:1337893	x	x				
615	SARS-CoV-2	GC376	Molnupiravir	Preclinical		Vero E6 cell	PMID:35889194	x	x				
616	ZIKV	Gemcitabine	Obatoclax	Preclinical		RPE cell	PMID:28049006	x		x			
617	FLUAV	Gemcitabine	Pimodivir	Preclinical		Human primary macrophages	PMID:27451344					x	
618	CVB-3	Gemcitabine	Ribavirin	Preclinical		Vero cell	PMID:26526589	x					
619	EV-A71	Gemcitabine	Ribavirin	Preclinical		Vero cell	PMID:26526589	x					
620	ECHOV-1	Gemcitabine	Rupintrivir	Preclinical		A549 cell	PMID:36146673			x			
621	ZIKV	Gemcitabine	Saliphenylhalamide	Preclinical		RPE cell	PMID:28049006	x		x			
622	MERS-CoV	Gemcitabine	Saracatinib	Preclinical		Huh-7 cell	PMID:29795047	x					
623	ECHOV-1	Gemcitabine	Vemurafenib	Preclinical		A549 cell	PMID:33080984	x					
624	EBOV	Genistein	Tyrphostin	Preclinical		HEK293 cell	PMID:21947546	x					
625	LASV	Genistein	Tyrphostin	Preclinical		Vero cell	PMID:21947546	x					
626	HCV	Glecaprevir	Pibrentasvir		3	Human	PMID:29020583;32445613;NCT02651194					x	
627	SARS-CoV-2	Glucocorticoid	Thalidomide	0/1		Human	PMID:33333254;https://www.preprints.org/manuscript/202002.0395/v1					x	
628	HIV-1	Glycovir	Zidovudine		2	Human	NCT00000791						N/A
629	VACV	Glycyrrhizic Acid	Prostaglandin A1	Preclinical		L929 cell	PMID:9477119	x					
630	FLUAV	Glycyrrhizin	Ribavirin	Preclinical		Mice	PMID:26668995	x					
631	HCV	Grazoprevir	Ribavirin		2	Human	PMID:27291249;NCT01716156					x	
632	HCV	GS-9256	Tegobuvir		2	Human	NCT01072695						N/A
633	PV-1	Guanidine	N-Phenyl-N′-3-Hydroxyphenylthiourea(PTU-23)	Preclinical		FL cell	PMID:10757231			x			
634	CMV	Gw275175X	Maribavir	Preclinical		ARPEp cell	PMID:30040968		x				
635	EV-A71	GW5074	Itraconazole	Preclinical		RD cell	PMID:27353263	x		x			
636	ECHOV-1	Halofuginone	Rupintrivir	Preclinical		A549 cell	PMID:36146673			x			
637	HIV	HBY 097	Zidovudine		2	Human	PMID:9952383;NCT00002357					x	
638	ECHOV-1	Homoharringtonine	Rupintrivir	Preclinical		A549 cell	PMID:36146673			x			
639	HCV	Homoharringtonine	Sofosbuvir	Preclinical		Huh-7.5 cell	PMID:33080984						x
640	ECHOV-1	Homoharringtonine	Vemurafenib	Preclinical		A549 cell	PMID:33080984	x					
641	MERS-CoV	HR2P-M2	Interferon Beta	Preclinical		Mice	PMID:26164863					x	
642	SARS-CoV-2	Hydroxychloroquine	Lopinavir	Preclinical		Vero cell	PMID:33333292		x				
643	SARS-CoV-2	Hydroxychloroquine	Remdesivir	Preclinical		Vero cell	PMID:33333292			x			
644	HSV-1	Idoxuridine	Interferon Beta	Preclinical		Vero cell	PMID:2163462	x					
645	HIV	Indinavir	L-756423		2	Human	NCT00002452						N/A
646	HIV	Indinavir	Nelfinavir	0/1		Human	NCT00002375						N/A
647	HIV	Indinavir	Ritonavir		2	Human	NCT00002361						N/A
648	HSV-1	Indomethacin	Interferon Alpha	Preclinical		Raji;Raji-HSV cell	PMID:1964373					x	
649	EBOV	Interferon Alpha	Interferon Beta	Preclinical		293T cell	PMID:26752302	x					
650	HSV-1	Interferon Alpha	Interferon Gamma	Preclinical		Vero cell	PMID:1331251					x	
651	HSV-2	Interferon Alpha	Interferon Gamma	Preclinical		Vero cell	PMID:16772029	x					
652	SARS-CoV	Interferon Alpha	Interferon Gamma	Preclinical		Vero cell	PMID:17191018	x					
653	NoV	Interferon Alpha	Interferon Gamma	Preclinical		HG23 Cell	PMID:29753657					x	
654	HSV-1	Interferon Alpha	Interferon Gamma	Preclinical		Monkey	PMID:3929044	x					
655	HCV	Interferon Alpha	Interferon Lambda	Preclinical		Huh-7 cell	PMID:23274666	x	x				
656	HBV	Interferon Alpha	Lamivudine		4	Human	NCT02598063						N/A
657	HDV	Interferon Alpha	Lamivudine		2	Human	PMID:16677149					x	
658	EBOV	Interferon Alpha	Lamivudine	Preclinical		293T cell	PMID:26752302	x					
659	SARS-CoV-2	Interferon Alpha	Lopinavir	0/1		Human	ChiCTR2000030535						N/A
660	HCV	Interferon Alpha	Mizoribine	Preclinical		OR6 cell	PMID:15809077					x	
661	HCV	Interferon Alpha	Mycophenolic Acid	Preclinical		Huh-7 cell	PMID:17101321	x					
662	HBV	Interferon Alpha	Myrcludex B		2	Human	NCT02637999						N/A
663	HCV	Interferon Alpha	NIM811	Preclinical		Unknown	PMID:21255610;PMID:16940091					x	
664	HCV	Interferon Alpha	Nitazoxanide		2	Human	NCT00418054						N/A
665	FLUAV	Interferon Alpha	Oseltamivir		2	Human	NCT01146535						N/A
666	HBV	Interferon Alpha	Pam3CSK4	Preclinical		PHH;HepaRG cell	PMID:35963549					x	
667	HSV-1	Interferon Alpha	Prostaglandin D2	Preclinical		Unknown	PMID:6100083	x					
668	HBV	Interferon Alpha	Rep 2139		2	Human	NCT02233075					x	
669	HBV	Interferon Alpha	Rep 2139-Ca		2	Human	PMID:27257978;NCT02646189					x	
670	HBV	Interferon Alpha	Resveratrol		2	Human	PMID:33407619;NCT03546530						x
671	HBV	Interferon Alpha	Ribavirin		3	Human	NCT00114361						N/A
672	HCV	Interferon Alpha	Ribavirin		4	Human	NCT00255034						N/A
673	HBV	Interferon Alpha	Ribavirin		2	Human	NCT00275938						N/A
674	HCV	Interferon Alpha	Ribavirin		4	Human	NCT00383864						N/A
675	HCV	Interferon Alpha	Ribavirin		2	Human	NCT00656006						N/A
676	HCV	Interferon Alpha	Ribavirin		4	Human	NCT01045278;NCT00383864;NCT00255034;NCT01447394;PMID:17470380;NCT00656006						N/A
677	HCV	Interferon Alpha	Ribavirin		3	Human	NCT01447394						N/A
678	BVDV	Interferon Alpha	Ribavirin	Preclinical		MDBK cell	PMID:12821481	x		x			
679	YFV	Interferon Alpha	Ribavirin	Preclinical		Vero cell	PMID:12821481	x		x			
680	HBV	Interferon Alpha	Ribavirin	Preclinical		FL cell	PMID:1328433	x					

681	SARS-CoV	Interferon Alpha	Ribavirin	Preclinical	Vero cell	PMID:15288617	x					
682	HBV	Interferon Alpha	Ribavirin	0/1	Human	PMID:15728914				x		
683	HCV	Interferon Alpha	Ribavirin	2	Human	PMID:17470380						x
684	NoV	Interferon Alpha	Ribavirin	Preclinical	HG23 Cell	PMID:17855555		x				
685	MERS-CoV	Interferon Alpha	Ribavirin	Preclinical	LLC-MK2 cell	PMID:23594967					x	
686	MERS-CoV	Interferon Alpha	Ribavirin	Preclinical	Vero cell	PMID:23594967					x	
687	MERS-CoV	Interferon Alpha	Ribavirin	Preclinical	Macaque	PMID:24013700					x	
688	HEV	Interferon Alpha	Ribavirin	Preclinical	Huh-7 cell	PMID:24145541	x					
689	HPV	Interferon Alpha	Ribavirin	0/1	Human	PMID:24661930					x	
690	MERS-CoV	Interferon Alpha	Ribavirin	0/1	Human	PMID:24831606					x	
691	MERS-CoV	Interferon Alpha	Ribavirin	0/1	Human	PMID:25278221					x	
692	SFTSV	Interferon Alpha	Ribavirin	Preclinical	Vero cell	PMID:26527529					x	
693	CHIKV	Interferon Alpha	Ribavirin	Preclinical	Vero cell	PMID:27496974	x					
694	ZIKV	Interferon Alpha	Ribavirin	Preclinical	Vero cell	PMID:29109164					x	
695	DENV	Interferon Alpha	Ribavirin	Preclinical	Huh-7 cell	PMID:29890736		x				
696	SARS-CoV-2	Interferon Alpha	Ribavirin	0/1	Human	PMID:33515771				x		
697	SARS-CoV-2	Interferon Alpha	Ribavirin	0/1	Human	PMID:32765274						x
698	EV-A71	Interferon Alpha	Rupintrivir	Preclinical	Vero cell	PMID:21536800	x					
699	HBV	Interferon Alpha	Shuanghuanglian	Preclinical	WISH;Vero cell	PMID:12525074	x					
700	HEV	Interferon Alpha	Sofosbuvir	Preclinical	PLC/PRF/5 cell	PMID:31362004		x				
701	HCV	Interferon Alpha	Taribavirin	2	Human	PMID:17470380						x
702	HCV	Interferon Alpha	Telaprevir	Preclinical	Huh-9-13;Huh-6;Huh5-2 cell	PMID:26036224		x				
703	HBV	Interferon Alpha	Tenofovir	4	Human	NCT01727271						N/A
704	EBOV	Interferon Alpha	Tenofovir	Preclinical	293T cell	PMID:26752302	x					
705	HBV	Interferon Alpha	Tenofovir	2	Human	PMID:30187599;NCT01706575					x	
706	HBV	Interferon Alpha	Thymosin Alpha 1	Preclinical	HepG2 cell	PMID:9722931					x	
707	EBOV	Interferon Alpha	Toremifene	Preclinical	293T cell	PMID:26752302	x					
708	HSV-1	Interferon Alpha	Trifluridine	Preclinical	Unknown	PMID:1318909	x					
709	HCV	Interferon Alpha	Valopicitabine	2	Human	NCT00118768						N/A
710	HSV-2	Interferon Alpha	Vidarabine	Preclinical	Mice	PMID:2455473					x	
711	HSV-1	Interferon Alpha	Vidarabine	Preclinical	Unknown	PMID:2987369	x	x				
712	HSV-2	Interferon Alpha	Vidarabine	Preclinical	Unknown	PMID:2987369	x	x				
713	VZV	Interferon Alpha	Vidarabine	Preclinical	HuEF cell	PMID:6329083	x	x				
714	HIV	Interferon Alpha	Zidovudine	1	Human	NCT00000967						N/A
715	EBOV	Interferon Alpha	Zidovudine	Preclinical	293T cell	PMID:26752302			x			
716	HBV	Interferon Beta	Interferon Gamma	Preclinical	HMF cell	PMID:1328409	x		x			
717	VZV	Interferon Beta	Interferon Gamma	Preclinical	Unknown	PMID:15604425	x					
718	HSV-1	Interferon Beta	Interferon Gamma	Preclinical	Vero cell	PMID:16099899;PMID:12388715	x					
719	SARS-CoV	Interferon Beta	Interferon Gamma	Preclinical	Vero cell	PMID:17191018	x					
720	HSV-1	Interferon Beta	Interferon Gamma	Preclinical	FB cell	PMID:18057251	x					
721	HSV-1	Interferon Beta	Interferon Gamma	Preclinical	Mice	PMID:19906941	x					
722	FLUAV	Interferon Beta	Interferon Lambda	Preclinical	A549;Calu-3 cell	PMID:25245230		x				
723	EBOV	Interferon Beta	Lamivudine	Preclinical	293T cell	PMID:26752302	x					
724	MERS-CoV	Interferon Beta	Mycophenolic Acid	Preclinical	Vero cell	PMID:24096239					x	
725	SARS-CoV-2	Interferon Beta	Remdesivir	2	Human	PMID:35762834					x	
726	HCV	Interferon Beta	Ribavirin	3	Human	NCT00249860						N/A
727	SARS-CoV	Interferon Beta	Ribavirin	Preclinical	Vero cell	PMID:15288617	x					
728	VSV	Interferon Beta	Ribavirin	Preclinical	Mice	PMID:25462341					x	
729	SFTSV	Interferon Beta	Ribavirin	Preclinical	Vero cell	PMID:26527529					x	
730	HEV	Interferon Beta	Sofosbuvir	Preclinical	PLC/PRF/5 cell	PMID:31362004		x				
731	EBOV	Interferon Beta	Tenofovir	Preclinical	293T cell	PMID:26752302	x					
732	EBOV	Interferon Beta	Toremifene	Preclinical	293T cell	PMID:26752302		x				
733	HIV	Interferon Beta	Zidovudine	3	Human	NCT00002238						N/A
734	EBOV	Interferon Beta	Zidovudine	Preclinical	293T cell	PMID:26752302	x					
735	NoV	Interferon Gamma	Interferon Lambda	Preclinical	HG23 Cell	PMID:29753657					x	
736	SARS-CoV	Interferon Gamma	Interleukin 4	Preclinical	Vero cell	PMID:16860835					x	
737	SFTSV	Interferon Gamma	Ribavirin	Preclinical	Vero cell	PMID:26527529					x	
738	HSV-1	Interferon Gamma	TNF Alpha	Preclinical	Hep-2 cell	PMID:8250541	x					
739	HSV-2	Interferon Gamma	TNF Alpha	Preclinical	Hep-2 cell	PMID:8250541	x					
740	SARS-CoV-2	Interferon Kappa	TFF2	0/1	Human	ChiCTR2000030262						N/A
741	FLUAV	Interferon Lambda	Oseltamivir	Preclinical	A549;Calu-3 cell	PMID:25245230	x					
742	HCV	Interferon Omega	Ribavirin	2	Human	NCT00097045						N/A
743	HCV	INX-08189	Ribavirin	2	Human	NCT01425970						N/A
744	DENV	INX-08189	Ribavirin	Preclinical	Huh-7 cell	PMID:25624323	x					
745	HIV-1	Islatravir	Lenacapavir	Preclinical	HEK293/17, TZM-gfp cell	PMID:35746673	x	x				
746	FLUAV	Isoprinosine	Rimantadine	Preclinical	Mice	PMID:1711269	x					
747	EV-A71	Itraconazole	Rupintrivir	Preclinical	RD cell	PMID:27353263	x					
748	EV-A71	Itraconazole	Suramin	Preclinical	RD cell	PMID:27353263			x			
749	SARS-CoV-2	Ivermectin	Niclosamide	Preclinical	Calu-3 cell	PMID:35717393		x				
750	SARS-CoV-2	Ivermectin	Niclosamide	Preclinical	Vero E6 cell	PMID:35717393	x	x				
751	SARS-CoV-2	Ivermectin	Remdesivir	Preclinical	Vero E6 cell	PMID:35093538	x					
752	MCV	Lactic Acid	Salicylic Acid	2	Human	PMID:22214282					x	
753	HBV	Lamivudine	Maraviroc	Preclinical	HepG2.2.15 cell	PMID:35238349	x		x			
754	HIV	Lamivudine	Nevirapine	0/1	Human	NCT03223402						N/A
755	HBV	Lamivudine	Oxymatrine	4	Human	NCT02202473						N/A
756	HBV	Lamivudine	Penciclovir	Preclinical	MDCK cell	PMID:8721544					x	
757	HIV	Lamivudine	Stavudine	3	Human	NCT00002371						N/A
758	HBV	Lamivudine	Telbivudine	2	Human	NCT00124241						N/A
759	HBV	Lamivudine	Tenofovir	Preclinical	AD38 cell	PMID:19374144		x				
760	EBOV	Lamivudine	Tenofovir	Preclinical	293T cell	PMID:26752302	x					

761	EBOV	Lamivudine	Toremifene	Preclinical	293T cell	PMID:26752302	x					
762	HIV	Lamivudine	Zidovudine	3	Human	NCT02181933						N/A
763	EBOV	Lamivudine	Zidovudine	Preclinical	293T cell	PMID:26752302	x					
764	HIV-1	Lamivudine	Minocycline	Preclinical	TZM-bl cell	PMID:33080984						x
765	HIV-1	Lamivudine	Monensin	Preclinical	TZM-bl cell	PMID:33080984	x					
766	HIV-1	Lamivudine	Rapamycin	Preclinical	TZM-bl cell	PMID:33080984						x
767	HIV-1	Lamivudine	Suramin	Preclinical	TZM-bl cell	PMID:33080984						x
768	FLUAV	Laninamivir	Pyruvaldehyde	Preclinical	MDCK cell	PMID:25523147	x					
769	SARS-CoV-2	Lapatinib	Remdesivir	Preclinical	MRC5-ACE2 cell	PMID:34871905	x					
770	HCV	Ledipasvir	Radalbuvir	Preclinical	GT1a cell	PMID:28882564	x					
771	HCV	Ledipasvir	Radalbuvir	Preclinical	GT1b cell	PMID:28882564		x				
772	HCV	Ledipasvir	Sofosbuvir	4	Human	NCT02480166						N/A
773	HIV-1;HCV	Ledipasvir	Sofosbuvir	3	Human	PMID:26196665					x	
774	HCV	Ledipasvir	Sofosbuvir	Preclinical	GT1a cell	PMID:28882564	x					
775	HCV	Ledipasvir	Sofosbuvir	Preclinical	GT1b cell	PMID:28882564	x					
776	YFV	Ledipasvir	Sofosbuvir	Preclinical	Huh-7 cell	PMID:31594756				x		
777	SARS-CoV-2	Ledipasvir	Sofosbuvir	N/A	Human	PMID:35449996					x	
778	HCV	Ledipasvir	Vedroprevir	Preclinical	GT1a cell	PMID:28882564		x				
779	HCV	Ledipasvir	Vedroprevir	Preclinical	GT1b cell	PMID:28882564		x				
780	BKV	Leflunomide	Sirolimus	Preclinical	HPTC	PMID:21079551					x	
781	HIV-1	Lenacapavir	Rilpivirine	Preclinical	HEK293/17, TZM-gfp cell	PMID:35746673	x	x				
782	CMV	Letermovir	Maribavir	Preclinical	ARPEp cell	PMID:30040968		x				
783	CMV	Letermovir	Maribavir	N/A	Human	PMID:35023177					x	
784	NoV	Levulinic Acid	Sodium Dodecyl Sulfate	Preclinical	Unknown	PMID:22856583					x	
785	EV-A71	LiCL	Teriflunomide	Preclinical	Vero cell	PMID:25412347	x					
786	SARS-CoV-2	Litonavir	Lopinavir	0/1	Human	ChiCTR2000029573						N/A
787	HDV	Lonafarnib	Myrcludex B	Preclinical	Mice	PMID:29950446					x	
788	HDV	Lonafarnib	Ritonavir	2	Human	NCT02430181						N/A
789	SARS-CoV-2	Lopinavir	Nitazoxanide	Preclinical	Vero cell	PMID:33333292	x		x			
790	SARS-CoV-2	Lopinavir	Ritonavir	4	Human	ChiCTR2000029308				x		
791	HPV	Lopinavir	Ritonavir	0/1	Human	ISRCTNRegistry48776874						N/A
792	HIV	Lopinavir	Ritonavir	4	Human	NCT00648999						N/A
793	MERS-CoV	Lopinavir	Ritonavir	Preclinical	Marmoset	PMID:26198719					x	
794	SARS-CoV-2	Lopinavir	Ritonavir	Preclinical	Vero cell	PMID:32759267						x
795	SARS-CoV-2	Lopinavir	Umifenovir	Preclinical	Vero cell	PMID:33333292	x					
796	TBEV	Luromarin	Meglumine Acetrizoate	Preclinical	SPEV cell	PMID:22359863					x	
797	CMV	Maribavir	S3I-201	Preclinical	MRC-5 cell	PMID:24070820	x					
798	CMV	Maribavir	Sirolimus	Preclinical	ARPEp cell	PMID:30040968	x					
799	CMV	Maribavir	Tomeglovir	Preclinical	MRC-5 cell	PMID:12323400	x					
800	CHIKV	Meclofenamic Acid	Ribavirin	Preclinical	Vero cell	PMID:26794398					x	
801	FLUAV	MEDI8852	Oseltamivir	2	Human	PMID:30150460;NCT02603952				x		
802	FLUAV	MEDS433	N4-Hydroxycytidine	Preclinical	A549 cell	PMID:36298835	x					
803	CHIKV	Mefenamic Acid	Ribavirin	Preclinical	Mice	PMID:26794398					x	
804	CHIKV	Mefenamic Acid	Ribavirin	Preclinical	Vero cell	PMID:26794398					x	
805	SARS-CoV-2	Melatonin	Mercaptopurine	Preclinical	In-silico	PMID:32194980	x					
806	MERS-CoV	Mercaptopurine	Mycophenolic Acid	Preclinical	N/A	PMID:25542975	x					
807	JUNV	Merimepodib	Ribavirin	Preclinical	Vero cell	PMID:29126899					x	
808	LASV	Merimepodib	Ribavirin	Preclinical	Vero cell	PMID:29126899					x	
809	ZIKV	Merimepodib	Ribavirin	Preclinical	Vero cell	PMID:29126899					x	
810	FLUAV	MI-701	Oseltamivir	Preclinical	MDCK cell	PMID:26022200	x					
811	RVFV	Midametinib	Rapamycin	Preclinical	H2.37 cell	PMID:29652799	x					
812	HIV-1	Minocycline	Tenofovir	Preclinical	TZM-bl cell	PMID:33080984						x
813	FLUAV	Mirdametinib	Oseltamivir	Preclinical	A549 cell	PMID:23523553	x					
814	SARS-CoV-2	Molnupiravir	Nafamostat	Preclinical	Calu-3 cell	PMID:36190406		x				
815	SARS-CoV-2	Molnupiravir	Nelfinavir	Preclinical	Vero E6 cell	PMID:33080984	x					
816	SARS-CoV-2	Molnupiravir	Nirmatrelvir	Preclinical	Calu-3 cell	PMID:35058606	x					
817	SARS-CoV-2	Molnupiravir	Nirmatrelvir	Preclinical	Vero E6 cell	PMID:35889194	x					
818	SARS-CoV-2	Molnupiravir	Nirmatrelvir	Preclinical	Mice	PMID:36209984					x	
819	SARS-CoV-2	Molnupiravir	Nirmatrelvir	Preclinical	Macaque	PMID:36263071					x	
820	SARS-CoV-2	Molnupiravir	Teriflunomide	Preclinical	Hamster	PMID:35492218					x	
821	SARS-CoV-2	Molnupiravir	Zapnometinib	Preclinical	Calu-3 cell	PMID:36145524	x					
822	HIV-1	Monensin	Tenofovir	Preclinical	TZM-bl cell	PMID:33080984	x					
823	SARS-CoV-2	MU-UNMC-2	SF2523	Preclinical	UNCN1T cell	PMID:35390226	x					
824	HEV	Mycophenolic Acid	Ribavirin	Preclinical	Huh-7 cell	PMID:24582714					x	
825	NoV	Mycophenolic Acid	Ribavirin	Preclinical	HG23 Cell	PMID:28807916		x				
826	NoV	Mycophenolic Acid	Tacrolimus	Preclinical	HG23 Cell	PMID:28807916		x				
827	MERS-CoV	Mycophenolic Acid	Tioguanine	Preclinical	N/A	PMID:25542975	x					
828	HBV	Myrcludex B	Tenofovir	2	Human	NCT03546621						N/A
829	SARS-CoV-2	N4-Hydroxycytidine	Orludodstat	Preclinical	Calu-3 cell	PMID:35492218	x					
830	SARS-CoV-2	N4-Hydroxycytidine	Orludodstat	Preclinical	Vero E6 cell	PMID:35492218	x					
831	SARS-CoV-2	N4-Hydroxycytidine	Teriflunomide	Preclinical	Calu-3 cell	PMID:35492218	x					
832	SARS-CoV-2	N4-Hydroxycytidine	Teriflunomide	Preclinical	Vero E6 cell	PMID:35492218	x					
833	SARS-CoV-2	N4-Hydroxycytidine	Vidofludimus	Preclinical	Calu-3 cell	PMID:35492218	x					
834	SARS-CoV-2	N4-Hydroxycytidine	Vidofludimus	Preclinical	Vero E6 cell	PMID:35492218	x					
835	HIV	Nelfinavir	Nevirapine	1	Human	NCT00002381						N/A
836	SARS-CoV-2	Nelfinavir	Remdesivir	Preclinical	Vero E6 cell	PMID:33080984	x					
837	HCV	Niclosamide	Sofosbuvir	Preclinical	Huh-7.5 cell	PMID:33080984	x					
838	SARS-CoV-2	Nirmatrelvir	Remdesivir	Preclinical	Mice	PMID:36209984				x		
839	SARS-CoV-2	Nirmatrelvir	Zapnometinib	Preclinical	Calu-3 cell	PMID:36145524	x					
840	FLUAV	Nitazoxanide	Oseltamivir	3	Human	NCT01610245						N/A

841	FLUBV	Nitazoxanide	Oseltamivir	3	Human	NCT01610245							N/A
842	FLUAV	Nitazoxanide	Oseltamivir	Preclinical	MDCK cell	PMID:25451059	x						
843	SARS-CoV-2	Nitazoxanide	Remdesivir	Preclinical	Vero cell	PMID:33333292	x						
844	SARS-CoV-2	Nitazoxanide	Ribavirin	2	Human	NCT04563208							N/A
845	NoV	Nitazoxanide	Ribavirin	Preclinical	Huh-7 cell	PMID:30104275	x						
846	SARS-CoV-2	Nitazoxanide	Umifenovir	Preclinical	Vero cell	PMID:33333292	x						
847	FLUAV	Nitazoxanide	Zanamivir	Preclinical	MDCK cell	PMID:25451059	x						
848	EV-A71	NITD008	NK-1.9K	Preclinical	RD;Vero;HEK293T cell	PMID:28063993	x						
849	WNV	NITD008	Vorinostat	Preclinical	Mice	PMID:26225754	x						
850	ECHOV-1	Obatoclax	Rupintrivir	Preclinical	A549 cell	PMID:36146673			x				
851	ZIKV	Obatoclax	Saliphenylhalamide	Preclinical	RPE cell	PMID:28049006	x		x				
852	ECHOV-1	Obatoclax	Vemurafenib	Preclinical	A549 cell	PMID:33080984	x						
853	SARS-CoV-2	Ombitasvir	Remdesivir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x						
854	SARS-CoV-2	Ombitasvir	Sofosbuvir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x						
855	SARS-CoV-2	Ombitasvir	Tenofovir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x						
856	FLUAV	Oseltamivir	Peramivir	Preclinical	MDCK cell	PMID:20633577	x	x					
857	FLUAV	Oseltamivir	Peramivir	Preclinical	Mice	PMID:20633577					x		
858	FLUAV	Oseltamivir	Pimodivir	Preclinical	MDCK cell	PMID:25547360	x						
859	FLUAV	Oseltamivir	Pimodivir	2	Human	PMID:30428049;NCT02342249					x		
860	FLUAV	Oseltamivir	Pomegranate	Preclinical	MDCK cell	PMID:19586764	x						
861	FLUAV	Oseltamivir	PUL-042	Preclinical	Mice	PMID:29066417					x		
862	FLUBV	Oseltamivir	PUL-042	Preclinical	Mice	PMID:29066417					x		
863	FLUAV	Oseltamivir	Pyruvaldehyde	Preclinical	MDCK cell	PMID:25523147	x						
864	FLUAV	Oseltamivir	Refametinib	Preclinical	A549 cell	PMID:23523553	x						
865	FLUAV	Oseltamivir	Ribavirin	Preclinical	Mice	PMID:17066897							x
866	FLUBV	Oseltamivir	Ribavirin	Preclinical	Mice	PMID:17066897					x		
867	FLUAV	Oseltamivir	Ribavirin	Preclinical	Mice	PMID:18725448	x						
868	FLUAV	Oseltamivir	Ribavirin	Preclinical	MDCK cell	PMID:19273672		x					
869	FLUAV	Oseltamivir	Ridostin	Preclinical	Mice	PMID:22145356					x		
870	FLUAV	Oseltamivir	Rimantadine	Preclinical	Mice	PMID:22617756;PMID:17176629	x						
871	SARS-CoV-2	Oseltamivir	Ritonavir	3	Human	NCT04261270							N/A
872	FLUAV	Oseltamivir	Selumetinib	Preclinical	A549 cell	PMID:23523553	x						
873	FLUAV	Oseltamivir	Simvastatin	Preclinical	Mice	PMID:25274854				x			
874	FLUAV	Oseltamivir	Zanamivir	Preclinical	MDCK cell	PMID:29079337					x		
875	CMV	Ouabain	Sunitinib	Preclinical	HFF cell	PMID:24277030	x						
876	SARS-CoV-2	Pamapimod	Pioglitazone	Preclinical	Calu-3; A549;TMPRSS2, Vero cell	PMID:35743273	x						
877	HIV	PEG IL-2	Zidovudine	0/1	Human	NCT00001997							N/A
878	SARS-CoV	Peptide	Peptide	Preclinical	Hela cell	PMID:18983873	x						
879	FLUAV	Peramivir	Pyruvaldehyde	Preclinical	MDCK cell	PMID:25523147	x						
880	FLUAV	Peramivir	Ribavirin	preclinical	Mice	PMID:12011541	x	x					
881	FLUAV	Peramivir	Ribavirin	Preclinical	Unknown	PMID:12011541	x						
882	FLUAV	Peramivir	Rimantadine	Preclinical	Mice	PMID:20943201;PMID:15561867	x						
883	SARS-CoV-2	Pibrentasvir	Remdesivir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144	x						
884	SARS-CoV-2	Pibrentasvir	Sofosbuvir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144		x					
885	SARS-CoV-2	Pibrentasvir	Tenofovir	Preclinical	Calu-3 cell,Vero E6	PMID:35194144		x					
886	FLUAV	Pimodivir	Zanamivir	Preclinical	MDCK cell	PMID:25547360	x						
887	SARS-CoV-2	Pinavir	Ritonavir	0/1	Human	ChiCTR2000030218							N/A
888	CCHFV	Plasma	Ribavirin	0/1	Human	PMID:21565949					x		
889	ECHOV-1	Pleconaril	Rupintrivir	Preclinical	A549 cell	PMID:36146673	x						
890	ECHOV-1	Pleconaril	Vemurafenib	Preclinical	A549 cell	PMID:36146673	x						
891	RVFV	Poly(ICLC)	Ribavirin	Preclinical	Mice	PMID:3662477					x		
892	FLUAV	Pyruvaldehyde	Zanamivir	Preclinical	MDCK cell	PMID:25523147	x						
893	SARS-CoV-2	Quercetin	Remdesivir	N/A	Human	PMID:34863994					x		
894	HCV	Radalbuvir	Sofosbuvir	Preclinical	GT1a cell	PMID:28882564	x						
895	HCV	Radalbuvir	Sofosbuvir	Preclinical	GT1b cell	PMID:28882564		x					
896	HCV	Radalbuvir	Vedroprevir	Preclinical	GT1a cell	PMID:28882564	x						
897	HCV	Radalbuvir	Vedroprevir	Preclinical	GT1b cell	PMID:28882564		x					
898	HIV-1	Rapamycin	Tenofovir	Preclinical	TZM-bl cell	PMID:33080984							x
899	HIV-1	Rapamycin	Valacyclovir	Preclinical	Mice	PMID:26374952					x		
900	HIV-1	Rapamycin	Valacyclovir	Preclinical	Mice	PMID:26374952					x		
901	RSV	RBI034	Ribavirin	Preclinical	Hep-2 cell	PMID:15168801					x		
902	ECHOV-1	Remdesivir	Rupintrivir	Preclinical	A549 cell	PMID:36146673		x					
903	SARS-CoV-2	Remdesivir	Sangivamycin	Preclinical	Caco-2 cell	PMID:34807849		x					
904	SARS-CoV-2	Remdesivir	Sangivamycin	Preclinical	Calu-3 cell	PMID:34807849		x					
905	SARS-CoV-2	Remdesivir	Sangivamycin	Preclinical	Vero E6 cell	PMID:34807849		x					
906	SARS-CoV-2	Remdesivir	SF2523	Preclinical	UNCN1T cell	PMID:35390226	x						
907	SARS-CoV-2	Remdesivir	Stenoparib	Preclinical	Vero E6 cell	PMID:36103462		x					
908	SARS-CoV-2	Remdesivir	Sulforaphane	Preclinical	Vero C1008 cell	PMID:35304580	x						
909	SARS-CoV-2	Remdesivir	Umifenovir	Preclinical	Vero cell	PMID:33333292	x		x				
910	SARS-CoV-2	Remdesivir	Zapnometinib	Preclinical	Calu-3 cell	PMID:36145524	x						
911	HBV	Rep 2139-Ca	Thymosin Alpha 1	2	Human	PMID:27257978;NCT02646189					x		
912	SINV	Ribavirin	Rimantadine	Preclinical	Chick Embryo Fibroblast	PMID:7434742					x		
913	FLUAV	Ribavirin	Rimantadine	Preclinical	MDCK cell	PMID:7447417					x		
914	PV-1	Ribavirin	Rupintrivir	Preclinical	Unknown	PMID:21466823	x	x					
915	FLUAV	Ribavirin	Selenazofurin	Preclinical	MDCK cell	PMID:3729336		x					
916	FLUBV	Ribavirin	Selenazofurin	Preclinical	MDCK cell	PMID:3729336		x					
917	YFV	Ribavirin	Selenazofurin	Preclinical	LLC-MK2 cell	PMID:6151377	x						
918	KHF	Ribavirin	Selenazofurin	Preclinical	Vero E6 cell	PMID:6151377		x					
919	JEV	Ribavirin	Selenazofurin	Preclinical	Vero 76 cell	PMID:6151377	x						
920	PICV	Ribavirin	Selenazofurin	Preclinical	Vero 76 cell	PMID:6151377	x						

921	RVFV	Ribavirin	Selenazofurin	Preclinical		Vero 76 cell	PMID:6151377		x				
922	VEEV	Ribavirin	Selenazofurin	Preclinical		Vero 76 cell	PMID:6151377	x					
923	HCV	Ribavirin	Silibinin		3	Human	NCT01871662						N/A
924	HEV	Ribavirin	Silvestrol	Preclinical		Huh-7 cell	PMID:30036559		x				
925	HCV	Ribavirin	Sofosbuvir		4	Human	NCT03069001						N/A
926	HEV	Ribavirin	Sofosbuvir	Preclinical		HEV3 cell	PMID:26408347		x				
927	HEV	Ribavirin	Sofosbuvir	Preclinical		PLC/PRF/5 cell	PMID:31362004		x				
928	NoV	Ribavirin	Tacrolimus	Preclinical		HG23 Cell	PMID:28807916		x				
929	JUNV	Ribavirin	Teriflunomide	Preclinical		Vero cell	PMID:29315647					x	
930	YFV	Ribavirin	Tiazofurin	Preclinical		LLC-MK2 cell	PMID:6151377	x					
931	JEV	Ribavirin	Tiazofurin	Preclinical		Vero 76 cell	PMID:6151377	x					
932	KHF	Ribavirin	Tiazofurin	Preclinical		Vero 76 cell	PMID:6151377		x				
933	NoV	Ribavirin	Tizoxanide	Preclinical		Huh-7 cell	PMID:30104275	x					
934	PV-1	Ribavirin	Vapendavir	Preclinical		Unknown	PMID:21466823	x		x			
935	HCV	Ribavirin	VX-135		2	Human	NCT01726946						N/A
936	FLUAV	Ribavirin	Zanamivir	Preclinical		MDCK cell	https://journals.sagepub.com/doi/pdf/10.1177/0956320295006002 05						N/A
937	FLUAV	Rimantadine	Selenious Acid	Preclinical		Unknown	PMID:3445584					x	
938	HIV	Ritonavir	Saquinavir		2	Human	PMID:17898705;NCT00000913						x
939	HIV	Ritonavir	Tipranavir		3	Human	NCT00440271						N/A
940	SARS-CoV-2	Ritonavir	Zapnometinib	Preclinical		Calu-3 cell	PMID:36145524	x					
941	HBV	RNAi	Entecavir		2	Human	NCT02452528						N/A
942	EV-A71	Rupintrivir	Suramin	Preclinical		RD cell	PMID:27353263		x				
943	EV-A71	Rupintrivir	Vapendavir	Preclinical		Unknown	PMID:21466823	x		x			
944	HRV-B14	Rupintrivir	Vapendavir	Preclinical		Unknown	PMID:21466823	x		x			
945	PV-1	Rupintrivir	Vapendavir	Preclinical		Unknown	PMID:21466823	x	x				
946	ECHOV-1	Rupintrivir	Vemurafenib	Preclinical		A549 cell	PMID:36146673	x					
947	HCV	Ruzasvir	Uprifosbuvir		2	Human	PMID:31108015;NCT02956629					x	
948	HIV	Saquinavir	Zalcitabine		2	Human	PMID:10682127;NCT00002333					x	
949	JEV	SCH16	Mycophenolic Acid	Preclinical		Porcine Stable Kidney	PMID:22738253	x					
950	JEV	SCH16	Pentoxifylline	Preclinical		Porcine Stable Kidney	PMID:22738253			x			
951	JEV	SCH16	Ribavirin	Preclinical		Porcine Stable Kidney	PMID:22738253	x					
952	YFV	Selenazofurin	Tiazofurin	Preclinical		LLC-MK2 cell	PMID:6151377		x				
953	JEV	Selenazofurin	Tiazofurin	Preclinical		Vero 76 cell	PMID:6151377		x				
954	KHF	Selenazofurin	Tiazofurin	Preclinical		Vero 76 cell	PMID:6151377		x				
955	EBOV	Sertraline	Toremifene	Preclinical		Huh-7 cell	PMID:29939303	x					
956	EBOV	Sertraline	Toremifene	Preclinical		Mice	PMID:33801811;PMID:29939303						x
957	HCV	Simeprevir	Sofosbuvir		4	Human	NCT02168361,PMID:25557952;NCT03069001					x	
958	HBV	Simvastatin	Tenofovir		1	Human	NCT00994773						N/A
959	CHIKV	SiRNA	SiRNA	Preclinical		Mice	PMID:24040429					x	
960	CHIKV	SiRNA	SiRNA	Preclinical		Vero cell	PMID:24040429		x				
961	HCV	Sofosbuvir	Telaprevir	Preclinical		Huh-7 cell	PMID:27035622	x	x	x			
962	HCV	Sofosbuvir	Vedroprevir	Preclinical		GT1a cell	PMID:28882564	x					
963	HCV	Sofosbuvir	Vedroprevir	Preclinical		GT1b cell	PMID:28882564		x				
964	HCV	Sofosbuvir	Velpatasvir		3	Human	PMID:26571066;NCT02201940;PMID:30203225					x	
965	SARS-CoV-2	Sofosbuvir	Velpatasvir	N/A		Human	PMID:35388092					x	
966	Rov	Sophora Flavescens Extract	Stevioside	Preclinical		Piglet	PMID:24704033					x	
967	HIV	Stavudine	Timunox		3	Human	NCT00002109						N/A
968	HIV-1	Suramin	Tenofovir	Preclinical		TZM-bl cell	PMID:33080984						x
969	HPIV-3	Suramin	Zanamivir	Preclinical		LLC-MK2 cell	PMID:27053240	x					
970	HCV	Tegobuvir	Telaprevir	Preclinical		Huh-9-13;Huh-6;Huh5-2 cell	PMID:26036224		x				
971	HBV	Telbivudine	Tenofovir		3	Human	NCT00805675;PMID:30601336					x	
972	HBV	Telbivudine	Tenofovir	Preclinical		AD38 cell	PMID:19374144		x				
973	HBV	Telbivudine	Valtorcitabine		2	Human	NCT00128544						N/A
974	EBOV	Tenofovir	Toremifene	Preclinical		293T cell	PMID:26752302	x					
975	HBV	Tenofovir	Vesatolimod		2	Human	PMID:29851204;NCT02579382						x
976	EBOV	Tenofovir	Zidovudine	Preclinical		293T cell	PMID:26752302	x					
977	HIV	Timunox	Zidovudine		3	Human	NCT00002109						N/A
978	EBOV	Toremifene	Zidovudine	Preclinical		293T cell	PMID:26752302	x					
979	KSHV	Valganciclovir	Zidovudine		2	Human	PMID:21487108					x	
980	HIV	Zalcitabine	Zidovudine	0/1		Human	NCT00002081						N/A



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