Tropical Journal of Pharmaceutical Research April 2025; 24 (4): 493-501
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
https://dx.doi.org/10.4314/tjpr.v24i4.6

Original Research Article

Inhibitory effect of emododstat on respiratory syncytial virus

San Li[1,2], Hui-Ming Dang[1,2], Shan Xu[2], Lei Liu[1]*, Yi-gang Tong[1,2]
[1]Jiamusi University School of Basic Medicine, Jiamusi 154007, [2]Beijing Advanced Innovation Center for Soft Matter Science and Engineering, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing 100029, China

For correspondence: **Email: liuleitianxue@163.com; **Tel:** 0086-0454-8618295*

Sent for review: 22 February 2025 *Revised accepted: 16 April 2025*

Abstract

Purpose: *To identify anti-respiratory syncytial virus (RSV-A) candidates from the pool of approved drugs through drug repositioning and preliminary elucidation of their mechanisms of action.*
Methods: *Human laryngeal epithelial carcinoma cells (HEp-2) were infected with RSV-A (GenBank: PQ594188). The cytopathic effect (CPE) was used to conduct an initial screening of 1213 compounds from the drug library. For the selected candidate drug, emvododstat, a dihydroorotate dehydrogenase (DHODH) inhibitor, further analysis was performed with Cell Counting Kit-8 (CCK-8) assay to determine the viral copy number using absolute quantification and to measure the half-maximal effective concentration (EC_{50}), half-maximal cytotoxic concentration (CC_{50}), and selectivity index ($SI = CC_{50}/EC_{50}$). A time-of-addition assay (TOA) was conducted to determine the phase of the antiviral action, and the potential mechanism involved was determined, in addition to the DHODH inhibitory properties of the drug.*
Results: *Emvododstat exhibited potent anti-RSV-A activity with an EC_{50} of 5.23 nmol/L and SI > 19,120 thereby outperforming Ribavirin (EC_{50} = 14.5 μmol/L, SI = 52). The TOA assays revealed that Emvododstat primarily acted during the post-entry phase, with minimal inhibition of viral entry.*
Conclusion: *This study has demonstrated, for the first time, that Emvododstat exerts nanomolar inhibitory activity and high selectivity against RSV-A viruses. This finding highlights the potential of drug repositioning strategies in antiviral drug development. Although its mechanism of action has not been fully clarified, the high selectivity and low cytotoxicity of Emvododstat provide an important basis for its clinical application.*

Keywords: *Emvododstat, Respiratory syncytial virus, Drug repositioning, DHODH inhibitor, Antiviral activity*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Human respiratory syncytial virus (RSV), a predominant etiological agent of acute lower respiratory tract infections worldwide, is taxonomically classified under the genus Orthopneumovirus within the family *Pneumoviridae*. The virus (RSV) was first isolated in 1955 from a chimpanzee suffering from respiratory disease [1], and in 1957, it was successfully isolated from humans, initially from an infant with severe respiratory illness [2]. The virus primarily spreads through respiratory droplets or direct contact. After infection, the immune response typically develops within 3 to 7 days, with clinical manifestations such as fever,

rhinorrhea, wheezing, chest tightness, and cough. Respiratory syncytial virus is the major pathogen that causes lower respiratory tract infections in infants and young children worldwide [3].

Contemporary clinical management continues to prioritize economically burdensome prophylactic monoclonal antibody (mAb) interventions, thereby perpetuating systemic disparities in the affordability of therapy across socioeconomic strata. For instance, the recommended dose of Palivizumab is 15 mg/kg, and the price of 50 mg of the drug is approximately $ 1,455 [4]. Nirsevimab is priced between $ 125 and $ 1,736 per dose [5], and its efficacy is limited in already infected patients [6]. Thus, the development of new and affordable anti-RSV drugs remains a critical and unsolved challenge.

Emvododstat is a small molecule initially identified as an inhibitor of VEGFA mRNA translation, and it is primarily used in the clinical treatment of cancers [7]. It has also shown some efficacy in the treatment of COVID-19 [8]. Subsequent studies revealed that Emvododstat is a potent inhibitor of dihydroorotate dehydrogenase (DHODH) [9]. By inhibiting DHODH, it disrupts the *de novo* synthesis of pyrimidines, leading to cell cycle arrest and suppression of abnormal proliferation of cancer cells and virus-infected cells [10]. However, to date, no studies have been carried out to determine the effectiveness of Emvododstat in the treatment of RSV.

EXPERIMENTAL

Materials

Human laryngeal epithelial carcinoma cells (HEp-2 cells) were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). Human respiratory syncytial virus (RSV) was isolated in 2023 from two throat swab samples collected from RSV-positive patients at Beijing Children's Hospital. The full genome sequence of the virus was obtained through high-throughput sequencing. The genomic sequences were submitted to GenBank with accession numbers: Type A: PQ594188 and Type B: PQ594189. Studies have shown that RSV Type A causes more severe symptoms than Type B [11], with Type A exhibiting higher virulence, based on which it was selected for subsequent experiments. The RSV RNA was extracted and reverse-transcribed using Super FastPure Cell RNA Kit, and the G protein gene sequence was amplified with polymerase chain reaction (PCR). The RSV plasmids were synthesized by Beijing Ruibo Xingke Biotechnology Company.

Reagents and instruments

Antiviral Drug Library (catalog no. L1700) was provided by TargetMol. This library consists of 1,213 compounds with known or potential antiviral activities, and it serves as an important tool for screening novel antiviral drugs. Emvododstat is one of the compounds included in the library. Viral RNA was extracted using Super FastPure Cell RNA Kit (item no. RC102-C1). Then reverse transcription was performed using HiScript Ⅱ Q RT SuperMix for qPCR (item no. R223-01), and finally real-time fluorescence quantitative PCR (qPCR) was done with Taq Pro Universal SYBR qPCR Master Mix (Q712-02). The three reagents (C102-C1, R223-01 and C102-C1) were purchased from Novozymes (Vazyme, China). Cytotoxicity was determined using Cell Counting Kit-8 (CCK-8) purchased from Biosharp, China. Primers and viral plasmids were synthesized by Beijing Ruibo Xingke Biotechnology Company. The primer sequences used were as follows:

Upstream primer sequence: 5' ATCATCGTGCTTATACAAGTTAAATCTT 3'

Downstream primer sequence: 5' TATGATTGCAGTTGTTAGTGTGAC 3'

Moreover, PCR amplifier with microcentrifuge (Eppendorf, Germany), real-time fluorescence quantitative PCR instrument (Thermo Fisher Scientific, USA), multifunctional enzyme labeler (BilTek, USA), and Invitrogen Qubit4 fluorometer (Thermo Fisher Scientific, USA) were also used in this study.

Methods

Plaque assay for viral titer

The HEp-2 cells were inoculated into 6-well plates and infected with a 10-fold gradient dilution of RSV-A virus solution when the cell density reached 70 – 80 %. After a 2-h infection period, the viral solution was removed, and the cells were washed three times with phosphate-buffered saline (PBS). Then, 2 mL of medium containing 1 % low-melting-point agarose was added, and the plates were incubated at 37 °C for 3 days. After fixation in 4 % paraformaldehyde for more than 2 h, the agarose overlay was removed, and the cells were stained with crystal violet solution for 5 min. Thereafter excess crystal violet stain was washed away with

water. The viral titer (PFU/mL) was calculated based on the number of plaques.

Viral replication curve assay

The RSV was used to infect HEp-2 cells at multiplicities of infection (MOI) of 0.1 and 0.01. At various time points, supernatants and viral RNA were collected for absolute quantification of viral copies with qPCR using Super FastPure Cell RNA Kit (Novozymes, China). The concentration of RSV plasmids was measured using the Invitrogen Qubit4 Fluorometer. A 10-fold serial dilution of the plasmid was used to generate the standard curve for the qPCR reaction. The standard curve was plotted, with the plasmid copy number as the horizontal coordinate and the measured cycling threshold (Ct value) as the vertical coordinate. Based on the standard curve and the Ct values of the samples, the viral copy numbers (copies/μL) were calculated. This allowed for assessment of the RSV infection process in HEp-2 cells and the proliferation of progeny viruses. The optimal MOI and sampling time for the experiment were ultimately determined.

Preliminary screening for RSV-A drugs using the drug library

The HEp-2 cells were inoculated in 96-well plates. After 24 h of culture, the cells were treated with RSV-A virus (MOI = 0.01) and various compounds from the antiviral drug library, with a final drug concentration of 10 μmol/L. The cells were incubated with the virus and drug-containing medium for 1 h. Following incubation, the virus and drug solution were removed, and fresh medium containing 10 μmol/L of the respective drug was added to each well. The negative control and virus-only groups were treated with equivalent concentration of dimethyl sulfoxide (DMSO) in place of drugs. After 48 h, the cells were examined for cytopathic effects (CPE) under a microscope. Cells without significant CPE were subjected to further analysis, as shown in Figure 1.

Half effective concentration (EC_{50}) and half-maximal cytotoxic concentration (CC_{50})

The EC_{50} values for compounds that did not exhibit significant CPE in the preliminary screening were further determined using the viral copy number quantification method. Firstly, the drug was diluted 1:1 with the culture medium before mixing with RSV-A virus at an MOI of 0.01, followed by incubation for 1 hour. After mixing, the final drug concentration was set to range from 10 μmol/L to 19.5 nmol/L across 10 gradient concentrations. After incubation, the medium was replaced with fresh medium containing only the drug. Following 48 hours of drug treatment, total RNA was extracted from the cells and reverse-transcribed using the Super FastPure Cell RNA kit. Then, the viral copy numbers were determined using the same method described above, and the viral inhibition rate (V) was calculated using Eq 1. Simultaneously, the cytotoxicity of each of the drugs (Eq 2) was assessed using the CCK-8 method. Absorbance (A) at 450 nm was recorded, and CC_{50} was calculated according to the kit manufacturer's instructions (Eq 1).

$$V\ (\%) = ((Cc-Cd)/Cc)100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

where Cc is the average copy number of positive control group, while Cd is the average copy number of drug group

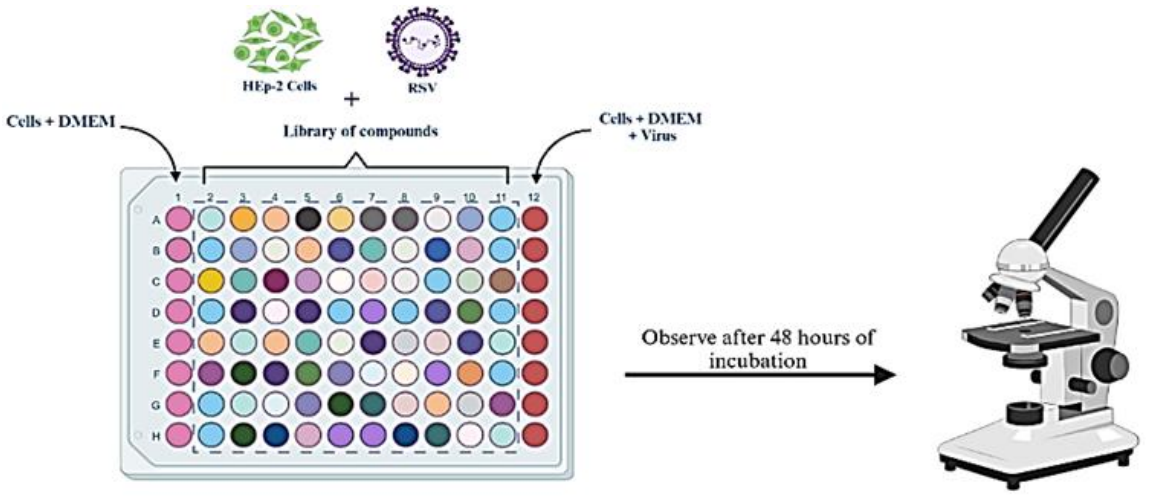

Figure 1: Drug Pre-Screening Flowchart

Cytotoxicity (%) = $\{\frac{A\,(\text{no drug}) - A\,(\text{drug})}{A\,(\text{no drug}) - A\,(\text{blank})}\}100$ ..... (2)

where *A (drug)* is absorbance value of the well containing cells, medium, CCK-8 solution, and drug solution; *A (blank)* is absorbance value of the well containing medium and CCK-8 solution, but without cells, and *A (no drug)* is absorbance value of the well containing cells, medium and CCK-8 solution, without drug solution.

Time-of-addition (TOA) assay

Based on different stages of virus infection in cells, the drug treatment times were divided into three groups: the Entry group, the post-entry group, and the Full-time group. In the Entry group, the drug was added at the time of viral entry into the cells. In the post-entry group, the drug was added 2 h after the virus had entered the cells, while in the Full-time group, the drug was added throughout the entire viral infection process. Additionally, a positive control group (PC group) was set up.

Super FastPure Cell RNA kit was used for the extraction of viral RNA for calculation of viral inhibition rate. The supernatants obtained were collected, serially diluted, and the viral titer of each group was determined using the plaque assay.

RESULTS

Conditions and preliminary screening of drugs with CPE

The viral titer of the RSV strain was determined using the plaque assay, is shown in Figure 2. The viral titer for this batch was approximately 5 × 10^5 PFU/mL. Next, the replication dynamics of RSV were analyzed with absolute quantification using qPCR. The results showed that, regardless of whether the MOI was 0.01 or 0.1, the viral load peaked at 48 h post-infection (Figure 3). The viral copy numbers significantly increased from 12 h post-infection, indicating that RSV had high replication efficiency in HEp-2 cells. Based on these results, the experimental conditions used were MOI of 0.01, and samples were collected after 48 hours of incubation.

Drugs from the initial screening that did not exhibit significant CPE were compared with the control groups. The results of this comparison are shown in Figure 5. After RSV infection, syncytia formation was observed in the infected cells, but no significant changes were seen in the drug-treated groups and the negative control group.

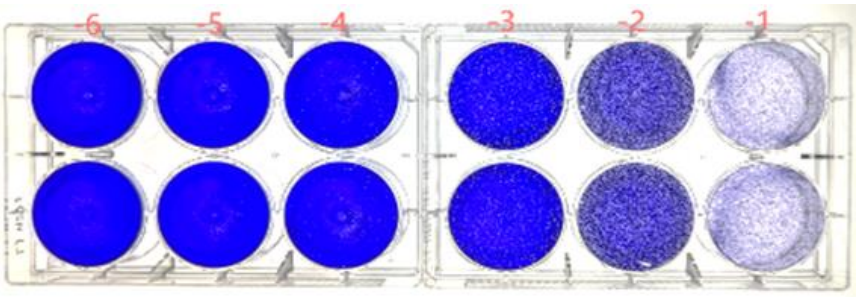

Figure 2: Results from virus titration assay

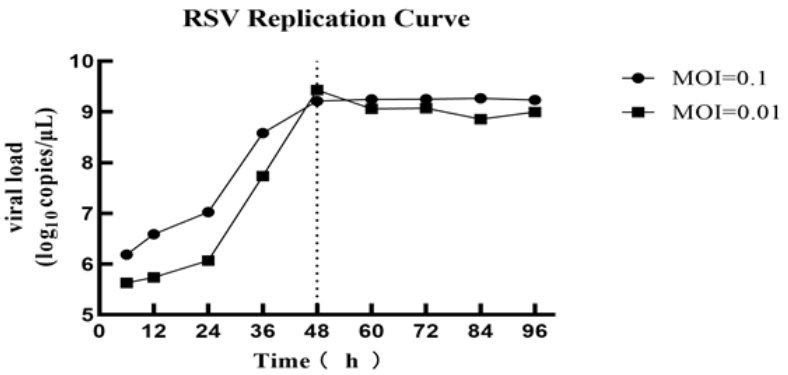

Figure 3: Replication dynamics of RSV-A virus in HEp-2 cells (based on absolute quantification with qPCR, R^2 = 0.999, EFF % = 88.935 %)

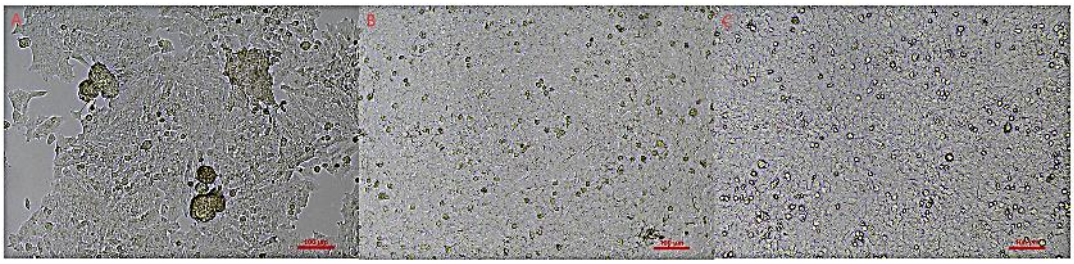

Figure 4: Complete inhibition of CPE by Emvododstat. (A) Virus-infected HEp-2 cells without drug treatment showed typical CPE after 48 h, (B) 10 µmol/L of Emvododstat completely inhibited CPE in infected HEP-2 cells, (C) Normal HEp-2 cells uninfected with the virus

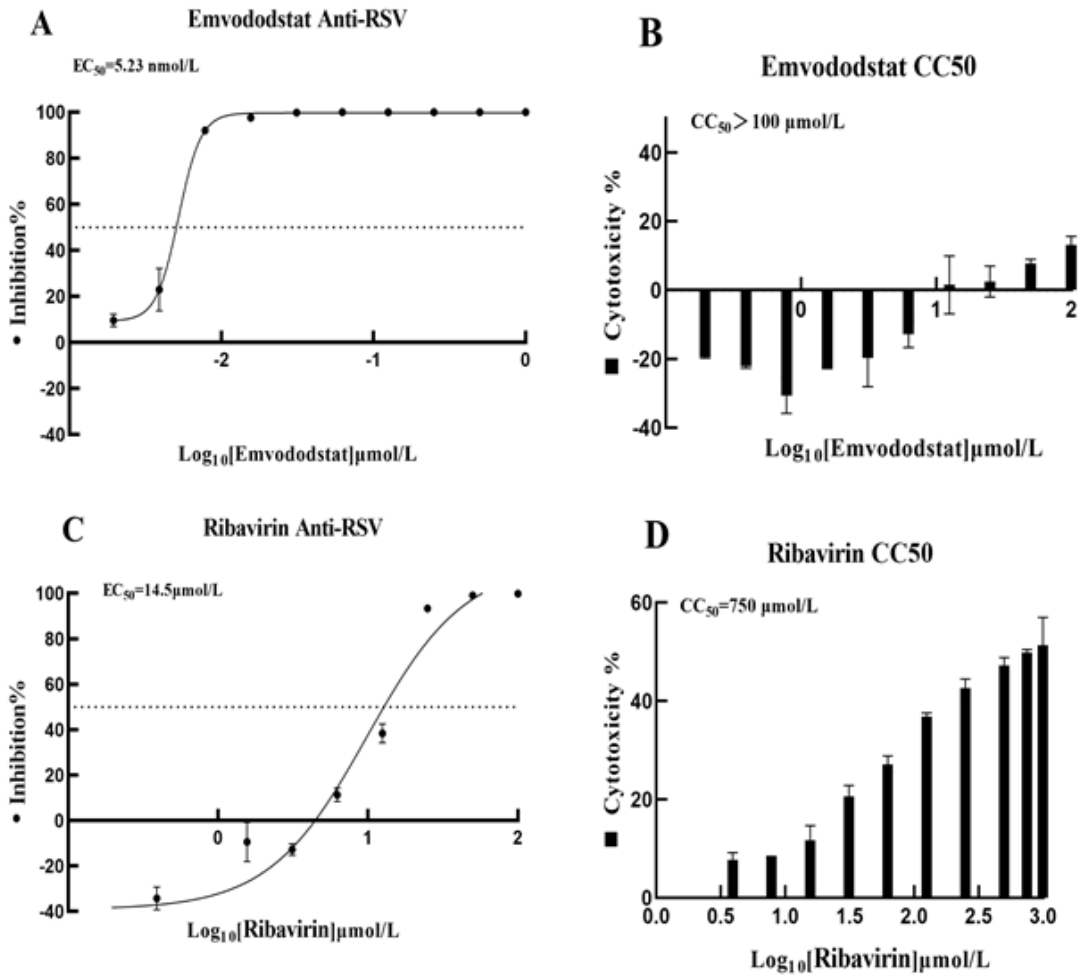

Figure 5: Comparison of antiviral effects of Emvododstat and Ribavirin against RSV (A) Emvododstat anti-RSV EC_{50}, (B) Emvododstat cytotoxicity (C) Ribavirin anti-RSV EC50; D: Ribavirin cytotoxicity

Antiviral activity of emvododstat

The experimental results showed that at a concentration of 19.5 nmol/L, Emvododstat inhibited more than 90% of viral replication. Therefore, the concentration was further reduced in a 10-step dilution series starting from 1 µmol/L, and the experiment was repeated. Similar results were observed for cytotoxicity measurements, where the cytotoxicity was less than 50% at a final concentration of 10 µmol/L. To improve the accuracy and reliability of the data, the experiment was repeated using a higher concentration of 100 µmol/L. The reference drug, Ribavirin, the reference drug, was also adjusted to the corresponding concentration. The results are shown in Figure 5.

Emvododstat demonstrated significant antiviral effects against RSV-A, with an EC_{50} value of

approximately 5.23 nmol/L, which was significantly lower than the corresponding EC_{50} for ribavirin (14.5 μmol/L). The selectivity index (SI = CC_{50}/EC_{50}) was greater than 19,120, indicating an extremely high therapeutic window. Thus, emvododstat showed promising potential as a novel drug for the treatment of RSV when compared to the traditional drug ribavirin.

Mechanism of antiviral effect of emvododstat

Three concentrations of 31.25, 15.63, and 7.81 nmol/L were selected for the pre-experiment based on the EC_{50} and CC_{50} obtained in the antiviral studies. The concentrations were prepared in duplicates for each group, and the results are shown in Figure 6. Drug concentration of 15.63 nmol/L was selected for the next plaque assay, and the results are shown in Figure 7. In the positive control (PC) group, the viral titer was approximately 3×10^6 PFU/mL. In the Entry group, the viral titer was approximately 4×10^5 PFU/mL, while in the post-entry group, the viral titer was approximately 1×10^4 PFU/mL. However, in the Full-time group, the viral titer was approximately 8×10^3 PFU/mL. The Entry group showed a limited reduction in viral titer, relative to the viral titer in the PC group, whereas the post-entry and Full-time groups showed a significant decrease.

Based on the results from drug addition experiments with phagocytosis, Emvododstat was significantly more effective in inhibiting RSV at the post-entry stage of virus entry (Post-entry group) and full-time administration (Full-time group) than at the entry stage of virus entry (Entry group). This observation suggests that Emvododstat may exert its inhibitory effect during a specific stage after the virus has entered the cell. However, the exact mechanism involved in this process requires further validation.

DISCUSSION

This study employed a drug repurposing strategy to screen potential novel antiviral agents against Respiratory Syncytial Virus (RSV) from an existing antiviral drug library. The results demonstrate that Emvododstat significantly inhibited RSV activity, with its Selectivity Index (SI) exceeding that of the traditional antiviral drug, ribavirin, by over 300-fold. Time-of-addition experiments further indicate that emvododstat exerted its antiviral effects primarily in the post-entry phase of the viral lifecycle, with limited inhibitory effects at high concentrations during the viral entry phase at high concentrations. This suggests that emvododstat probably exerts its inhibitory action after the virus has entered the host cell, although the precise molecular mechanism involved still requires further investigation. It has been shown that DHODH inhibitors, e.g., brequinar [12] and leflunomide [13] block viral proliferation by inhibiting *de novo* synthesis of pyrimidines and by limiting the supply of nucleotides required for viral genome replication. Studies have shown that emvododstat, a potent DHODH inhibitor, has demonstrated potential in regulating the cell cycle by inhibiting pyrimidine metabolism during the treatment of cancer [7] and COVID-19 [9]. Based on these findings, it may be speculated that the antiviral effect of emvododstat on RSV is due to inhibition of DHODH. The inhibition of DHODH indirectly interferes with the RNA replication process by limiting the pyrimidine pool in the host cell. However, this hypothesis requires further experimental validation through measurement of changes in levels of pyrimidine metabolites (e.g., UTP and CTP) in host cells treated with emvododstat, and comparing the antiviral effects and stages of action of emvododstat with other DHODH inhibitors (e.g., brequinar) against RSV.

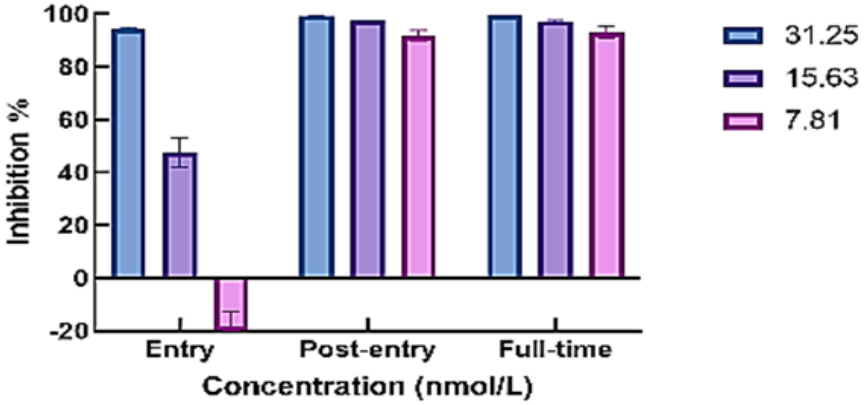

Figure 6: Results of the time-of-addition experiment for Emvododstat

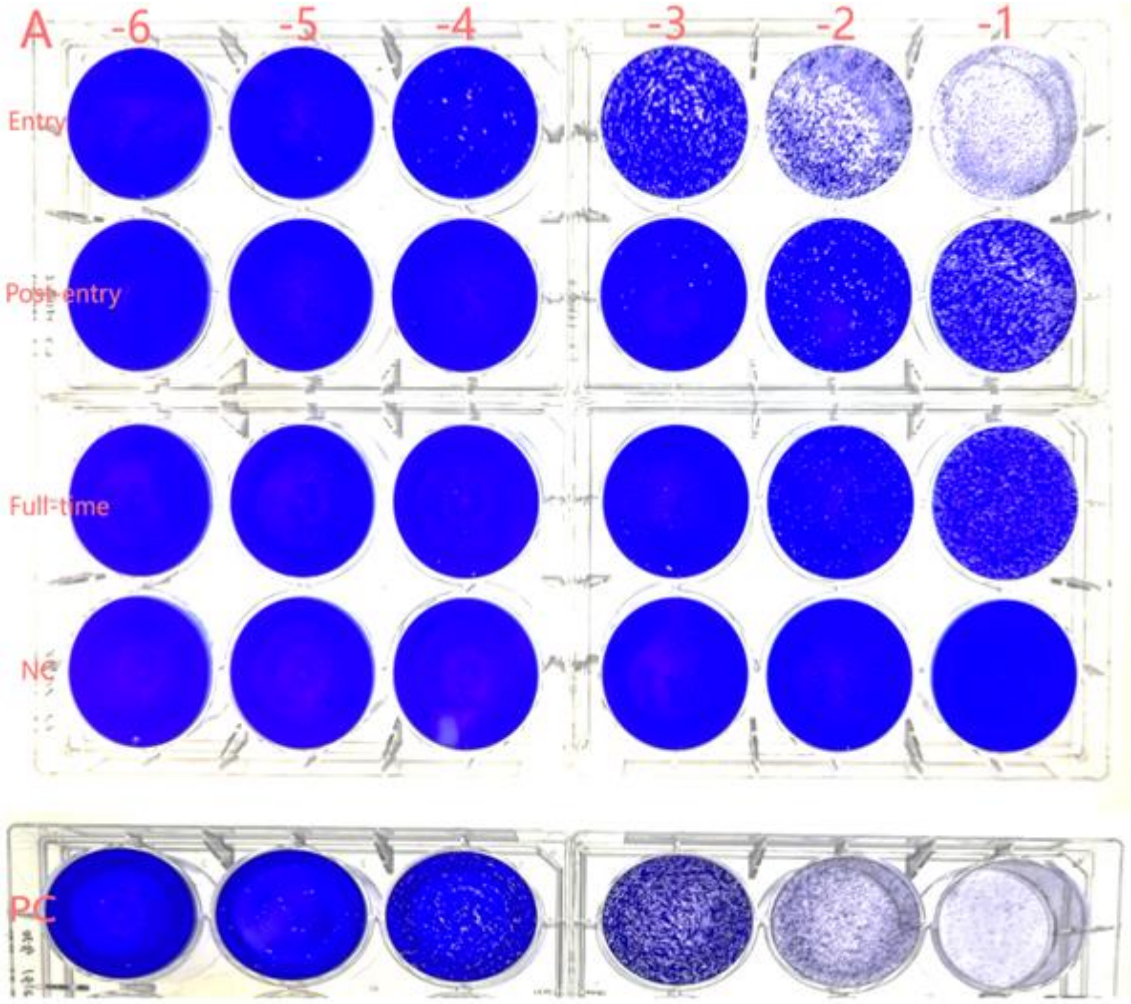

Figure 7: Plaque formation assay results of the time-of-addition experiment for Emvododstat

It is worth noting that, even during the viral entry phase, high concentrations of emvododstat still exhibited some inhibitory effects on RSV. This may be due to residual drug effects that indirectly influence subsequent viral replication and spread, rather than directly interfering with the mechanism of viral entry. Thus, some degree of viral suppression was observed despite administration only at the viral entry stage. This phenomenon could be further elucidated by monitoring the real-time impact of emvododstat on the viral entry process using fluorescently labeled viral particles.

In recent years, significant progress has been made in the prevention and treatment of RSV infections, including the development of multiple RSV vaccines [14,15] and the preventive drug, nirsevimab. However, RSV continues to pose a significant public health burden globally, especially among infants, the elderly, and immunocompromised patients. Despite the emergence of vaccines and monoclonal antibody therapies that offer new hope for RSV prevention and treatment, the therapeutic options for RSV remain limited. Therefore, the development of novel antiviral drugs for RSV remains an urgent scientific challenge.

The results of this study provide strong support for the application of drug repositioning strategies in the development of anti-RSV drugs. Relative to traditional drug development pathways, drug repositioning offers advantages such as lower development costs and shorter timelines, thereby allowing for screening and redevelopment based on existing drugs. This finding further validates the potential of drug repositioning in enhancing the efficiency and economic benefits of drug development efficiency and economic benefits, particularly when addressing the urgent need for antiviral drugs in public health.

Furthermore, the potential of emvodostat applications in various diseases [8,16,17] provides more opportunities for investigating its broad-spectrum antiviral activity. Therefore, future studies should expand their indications

and explore their potential in the treatment of other viral diseases, particularly their efficacy and mechanisms of action against other respiratory viruses. By broadening its applications, emvododstat has the potential to emerge as a valuable drug for combating a wide range of viral infections, including those with unmet medical needs in the respiratory disease sector. Given the current urgent demand for low-cost small-molecule antiviral drugs in the field of RSV treatment, emvododstat is expected to become a promising candidate for combination therapy in the fight against RSV. However, attention should also be paid to the side effects associated with the combination of medicines [18].

Limitations of this study

This study has some limitations. The experiments were conducted solely with RSV-A type virus. The inhibitory effects of emvododstat on RSV-B type were not evaluated. Moreover, the study was confined to *in vitro* cell models: there were no animal experiments. Thus, there are no data based on *in vivo* efficacy and safety. In addition, the direct causal relationship between DHODH inhibition and impaired RSV replication was not firmly established. Further studies should incorporate metabolomics analysis to study the dynamic changes in the pyrimidine pathway. The CRISPR technology should be used for creating DHODH-deficient cell models, and the *in vivo* antiviral efficacy of emvododstat should be validated in mouse RSV infection models.

CONCLUSION

This study, through drug repositioning strategies and related *in vitro* experiments, has demonstrated that emvododstat exhibited potent antiviral activity against RSV-A by significantly outperforming the traditional drug, ribavirin. Although its mechanism of action remains to be fully understood, its high selectivity and low cytotoxicity provide strong evidence for its clinical potential.

DECLARATIONS

Acknowledgement

We thank the School of Life Sciences, Beijing University of Chemical Technology, for the experimental and technical support. This study was supported by grant on the Mechanism of Anti-Neocoronavirus Action of Chikungunin (no. 82151224).

Conflict of interest

No conflict of interest associated with this work

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Use of Artificial Intelligence/large language models

We used ChatGPT to translate the original manuscript into English.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yi-gang Tong and Shan Xu conceived the study and provided the funding; San Li, Hui-Ming Dang performed the experiments and analyzed data; San Li wrote the manuscript. Yi-gang Tong, Shan Xu and Lei Liu modified the manuscript. Yi-gang Tong and Lei Liu served as supervisors. All authors reviewed the manuscript and approved the submitted version.

REFERENCES

1. *Blount RE, Morris JA, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. Proc Soc Exp Biol Med 1956; 92(3): 544-549.*
2. *Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). Isolation, properties and characterization. Am J Hyg 1957; 66(3): 281-290.*
3. *Shi T, David AM, Katherine LO, Eeic AFS, Shabir AM, Bradford D, Fernando PP, Evelyn B, Sozinho A, Claidia A. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017; 390(10098): 946-958.*
4. *Smart KA, Lanctôt KL, Paes BA. The cost effectiveness of palivizumab: a systematic review of the evidence. J Med Econ 2010; 13(3): 453-463.*
5. *Brown R, Sean T, Tsoi B, Cromwell I. Cost-effectiveness of nirsevimab for the prevention of respiratory syncytial virus infection in infants: CADTH health technology review. Canadian Agency for Drugs and Technologies in Health; 2023.*
6. *Geskey JM, Thomas NJ, Brummel GL. Palivizumab: a review of its use in the protection of high-risk infants*

against respiratory syncytial virus (RSV). Biol Targets Ther 2007; 1(1): 33-43.
7. Cao L, Weetall M, Trotta C, Cintron K, Ma J, Kim MJ, Furia B, Romfo C, Graci JD, Li W, et al. Targeting of hematologic malignancies with PTC299, a novel potent inhibitor of dihydroorotate dehydrogenase with favorable pharmaceutical properties. Mol Cancer Ther 2019; 18(1): 3-16.
8. Şimşek-Yavuz S, Komsuoğlu Çelikyurt FI. An update on anti-viral treatment of COVID-19. Turk J Med Sci 2021; 51(SI-1): 3372-3390.
9. Branstrom A, Cao L, Furia B, Trotta C, Santaguida M, Graci JD, Colacino JM, Ray B, Li W, Sheedy J, et al. Emvododstat, a potent dihydroorotate dehydrogenase inhibitor, is effective in preclinical models of acute myeloid leukemia. Front Oncol 2022; 12: 832816.
10. Ma J, Kaushik D, Yeh S, Northcutt V, Babiak J, Risher N, Weetall M, Moon YC, Welch EM, Molony L, et al. In vitro metabolism, pharmacokinetics and drug interaction potentials of Emvododstat, a DHODH inhibitor. Xenobiotica Fate Foreign Compd Biol Syst 2022; 52(2): 152-164.
11. Jafri HS, Wu X, Makari D, Henrickson KJ. Distribution of respiratory syncytial virus subtypes A and B among infants presenting to the emergency department with lower respiratory tract infection or apnea. Pediatr Infect Dis J 2013; 32(4): 335-340.
12. Chen Y, Guo Y, Chang H, Song Z, Wei Z, Huang Z, Zheng Z, Zhang G, Sun Y. Brequinar inhibits African swine fever virus replication in vitro by activating ferroptosis. Virol J 2023; 20(1): 242.
13. Kaur H, Sarma P, Bhattacharyya A, Sharma S, Chhimpa N, Prajapat M, Prakash A, Kumar S, Singh A, Singh R, et al. Efficacy and safety of dihydroorotate dehydrogenase (DHODH) inhibitors "leflunomide" and "teriflunomide" in COVID-19: A narrative review. Eur J Pharmacol 2021; 906: 174233.
14. Melgar M, Britton A, Roper LE, Talbot HK, Long SS, Kotton CN, Havers FP. Use of respiratory syncytial virus vaccines in older adults: recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep 2023; 72(29): 793-801.
15. Two vaccines (Arexvy and Abrysvo) for prevention of RSV disease. Med Lett Drugs Ther 2023; 65(1686): 155-156.
16. Luban J, Sattler RA, Mühlberger E, Graci JD, Cao L, Weetall M, Trotta C, Colacino JM, Bavari S, Strambio-De-Castillia C, et al. The DHODH inhibitor PTC299 arrests SARS-CoV-2 replication and suppresses induction of inflammatory cytokines. Virus Res 2021; 292: 198246.
17. Zhang L, Zhang J, Wang J, Ren C, Tang P, Ouyang L, Wang Y. Recent advances of human dihydroorotate dehydrogenase inhibitors for cancer therapy: Current development and future perspectives. Eur J Med Chem 2022; 232: 114176.
18. Rambe RE, Angela IFD, Khairunnisa K. Potential drug-drug interactions among outpatients with chronic diseases at an Indonesian teaching hospital. Trop J Pharm Res 2025; 24(2): 267-272.