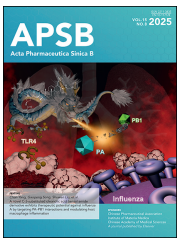
Acta Pharmaceutica Sinica B 2025;15(8):4322−4323

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



EDITORIAL

A5—A dual-target antiviral compound that rewrites the rules of influenza therapy

KEY WORDS

Influenza;
RNA-dependent RNA polymerase;
Dual-target therapy

Seasonal and pandemic influenza remains a formidable global health burden, with severe cases often exacerbated by uncontrolled viral replication and dysregulated host immune responses[1]. The high mutability of influenza viruses and the continuous emergence of drug-resistant strains underscore the urgent need for novel antiviral agents[2]. Amid this landscape, the report by Professor Liu and colleagues at Southern Medical University introduces **A5**—a chemically optimized oleanolic-acid derivative that strikes at two Achilles' heels of influenza by simultaneously targeting the viral PA−PB1 protein−protein interaction (PPI) of the viral RNA polymerase and the host TLR4–mediated inflammatory pathway[3]. By fusing direct antiviral potency with immunomodulatory control, **A5** transcends the limitations of single-target agents and establishes a new therapeutic paradigm.

Moreover, structural ingenuity underpins **A5**'s breakthrough activity. A scaffold-hopping maneuver replaced oleanolic acid's C-3 trisaccharide with an L-hydroxyproline-based aromatic linker, redirecting binding from the hemagglutinin (HA) surface protein to a hydrophobic crevice within the PA subunit.

The study addresses a critical challenge in influenza drug development: the difficulty of targeting the highly conserved yet hydrophobic binding pocket at the PA−PB1 interface of the viral polymerase[4]. Through a scaffold-hopping strategy, the team replaced the C-3 trisaccharide group of oleanolic acid with an L-hydroxyproline-derived rigid aromatic chain, which unexpectedly shifted the compound's target from the HA protein to the PA subunit. Molecular simulation dynamics analyses reveal that **A5** forms a robust network of hydrogen bonds and hydrophobic contacts that competitively disrupt PA−PB1 heterodimerization, thereby silencing viral genome replication.

Notably, this PA−PB1 protein−protein interaction (PPI) PPI-targeting mechanism delivers two decisive advantages[5]: (i) broad-spectrum efficacy against oseltamivir- and baloxavir-resistant strains, and (ii) a formidable genetic barrier—only a 2.6-fold shift in EC_{50} after 40 serial passages *versus* 22-fold for oseltamivir and 78-fold for baloxavir.

Equally compelling is **A5**'s host-directed activity. By antagonizing TLR4, **A5** dampens NF-κB signaling and the ensuing cytokine storm (*e.g.*, IL-6, TNF-α)[6]. In H1N1-challenged mice, combination therapy with oseltamivir (ZIP synergy score 12.78) rescued 100% of animals while markedly attenuating lung pathology. These data underscore the translational promise of a virus−host co-targeting strategy that both suppresses replication and shields tissues from immunopathology.

Yet the path to the clinic is not without obstacles. **A5**'s low aqueous solubility constrains oral bioavailability, a limitation the authors propose to surmount through prodrug design, side-chain refinement, or nanocarrier-enabled delivery. Rigorous pharmacokinetic optimization and comprehensive safety profiling will be essential to unlock **A5**'s full therapeutic potential.

In summary, Professor Liu and colleagues have transformed a natural-product scaffold into a precision-engineered, dual-target agent that redefines the antiviral armamentarium. **A5**'s unique confluence of high barrier to resistance, synergistic compatibility with existing drugs, and capacity to quell immunopathology provides a blueprint for next-generation influenza therapeutics, and potentially for tackling other respiratory viruses when host inflammation fuels disease severity.

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.07.033

Reference

1. Bay P, Martin Loeches I, Haudebourg AF, Lê MP, Peytavin G, Rameix Welti MA, et al. How to manage antivirals in critically ill patients with influenza?. *Clin Microbiol Infect* 2025;**31**:1157−65.
2. Liu C, Hu L, Dong G, Zhang Y, Ferreira DSE, Liu X, et al. Emerging drug design strategies in anti-influenza drug discovery. *Acta Pharm Sin B* 2023;**13**:4715−32.
3. Lu K, He J, Hong C, Li H, Ruan J, Wang J, et al. A novel C-3-substituted oleanolic acid benzyl amide derivative exhibits therapeutic potential against influenza a by targeting PA−PB1 interactions and modulating host macrophage inflammation. *Acta Pharm Sin B* 2025;**15**: 4156−73.
4. He X, Zhou J, Bartlam M, Zhang R, Ma J, Lou Z, et al. Crystal structure of the polymerase PA(C)−PB1(N) complex from an avian influenza H5N1 virus. *Nature* 2008;**454**:1123−6.
5. Massari S, Desantis J, Nizi MG, Cecchetti V, Tabarrini O. Inhibition of influenza virus polymerase by interfering with its protein−protein interactions. *ACS Infect Dis* 2021;**7**:1332−50.
6. Kim CU, Lim D, Kim YS, Ku B, Kim DJ. Influenza viral matrix 1 protein aggravates viral pathogenicity by inducing TLR4-mediated reactive oxygen species production and apoptotic cell death. *Cell Death Dis* 2023;**14**:228.

Shibo Jiang

Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai 200032, China

E-mail address: shibojiang@fudan.edu.cn