

Discovery of a novel influenza A virus inhibitor targeting a distinct pocket at the viral nucleoprotein dimer interface

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The Global Viral Infection Research Center (G VIC), a TOP TIER project of the National Research Foundation of Korea, aims to develop novel antivirals and vaccines through international collaboration. As part of this effort, the VirusBank Platform screened ~100,000 compounds from the Korea Research Institute of Chemical Technology (KRICT) to identify inhibitors of influenza virus using a MUNANA assay on A549 cells.

Here we report compound R91, a novel hit with potent anti influenza activity ($EC_{50} = 1.3 \mu M$, $CC_{50} > 25 \mu M$). R91 reduced vRNA levels by 5-log₁₀ in the supernatant of MDCK cells infected with A/PR/8/1934 (H1N1) at $6.4 \mu M$. Notably, the activity was restricted to the PR8 strain, with no detectable effects against other influenza A or B viruses.

Selection of resistant variants identified a substitution in the viral nucleoprotein (NP), completely abrogating antiviral activity and identifying NP as the target. Structural analysis of the NP protein placed the mutation within a druggable pocket at the NP dimer interface, adjacent to the binding site of nucleozin, a known NP-targeting influenza inhibitor. Interestingly, mutant viruses showed unchanged sensitivity to nucleozin. Moreover, time of addition assays revealed similar profiles for R91 and nucleozin, with loss of efficacy when added after ~6 h p.i.

These findings suggest that R91 interferes with NP–NP interactions, impairing ribonucleoprotein complex assembly and thereby inhibiting viral replication and transcription.

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Yes, I am a junior scientist.

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