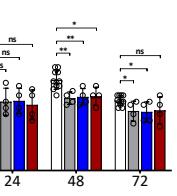


0 μ M 2.5 μ M 5 μ M 10 μ M

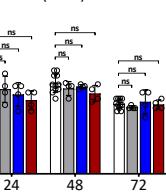
0 uM 0.0625 uM 0.125 uM 0.25 uM

0 μ M 0.25 μ M 0.5 μ M 1 μ M

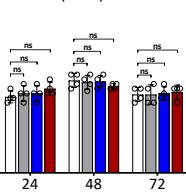
Erlotinib H1N1 (NL09)



Gefitinib H1N1 (NL09)



Gilteritinib H1N1 (NL09)



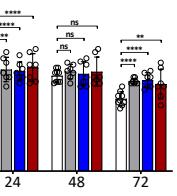
Hours post-infection	0 μM	0.025 μM	0.05 μM	0.1 μM
0	~0.2	~0.2	~0.2	~0.2
24	~8.0	~7.5	~6.5	~6.0
48	~8.0	~7.5	~7.0	~6.5
72	~7.0	~5.5	~5.0	~4.8

Detailed description: The figure is a bar chart titled 'H3N2 (NL11)' showing hemagglutination titers. The y-axis ranges from 0 to 9. The x-axis shows time points: 0, 24, 48, and 72 hours post-infection (hpi). For each time point, there are four bars representing different concentrations: 0 μM (white), 0.25 μM (light gray), 0.5 μM (blue), and 1 μM (red). Error bars are present on all bars. Statistical significance is indicated by brackets above the groups: a bracket between 0 hpi and 24 hpi covers the 0 μM, 0.25 μM, and 0.5 μM bars, with a label '***'; a bracket between 24 hpi and 48 hpi covers the 0.25 μM, 0.5 μM, and 1 μM bars, with a label '**'; and a bracket between 48 hpi and 72 hpi covers the 0.5 μM and 1 μM bars, with a label '****'.

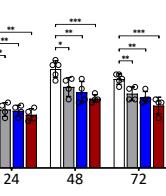
Hours post-infection (hpi)	0 μM	0.25 μM	0.5 μM	1 μM
0	0	0	0	0
24	0	~8.2	~8.2	~7.8
48	0	~8.2	~8.2	~7.8
72	0	~7.2	~6.8	~5.5

Hours post-infection (hpi)	0.0625 μ M	0.125 μ M	0.25 μ M
0	~100%	~100%	~100%
24	~100%	~100%	~100%
48	~100%	~100%	~100%
72	~100%	~100%	~100%

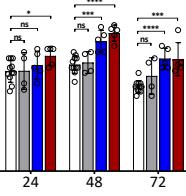
Lapatinib H1N1 (NL09)



Lenvatinib H1N1 (NL09)



Nintedanib



Detailed description: A bar chart showing the concentration of H3N2 (NL11) virus (TCID₅₀/mL) on the y-axis (log scale from 0 to 9) versus hours post-infection (hpi) on the x-axis (0, 24, 48, 72). Four groups of bars represent different concentrations: 0 μM (light gray), 2.5 μM (medium gray), 5 μM (blue), and 10 μM (red). Error bars represent standard deviation. Statistical significance relative to the 0 μM group is indicated by asterisks: ns (not significant) at 24 hpi for the 2.5 μM group, **** at 48 hpi for all groups, and **** at 72 hpi for the 5 μM and 10 μM groups.

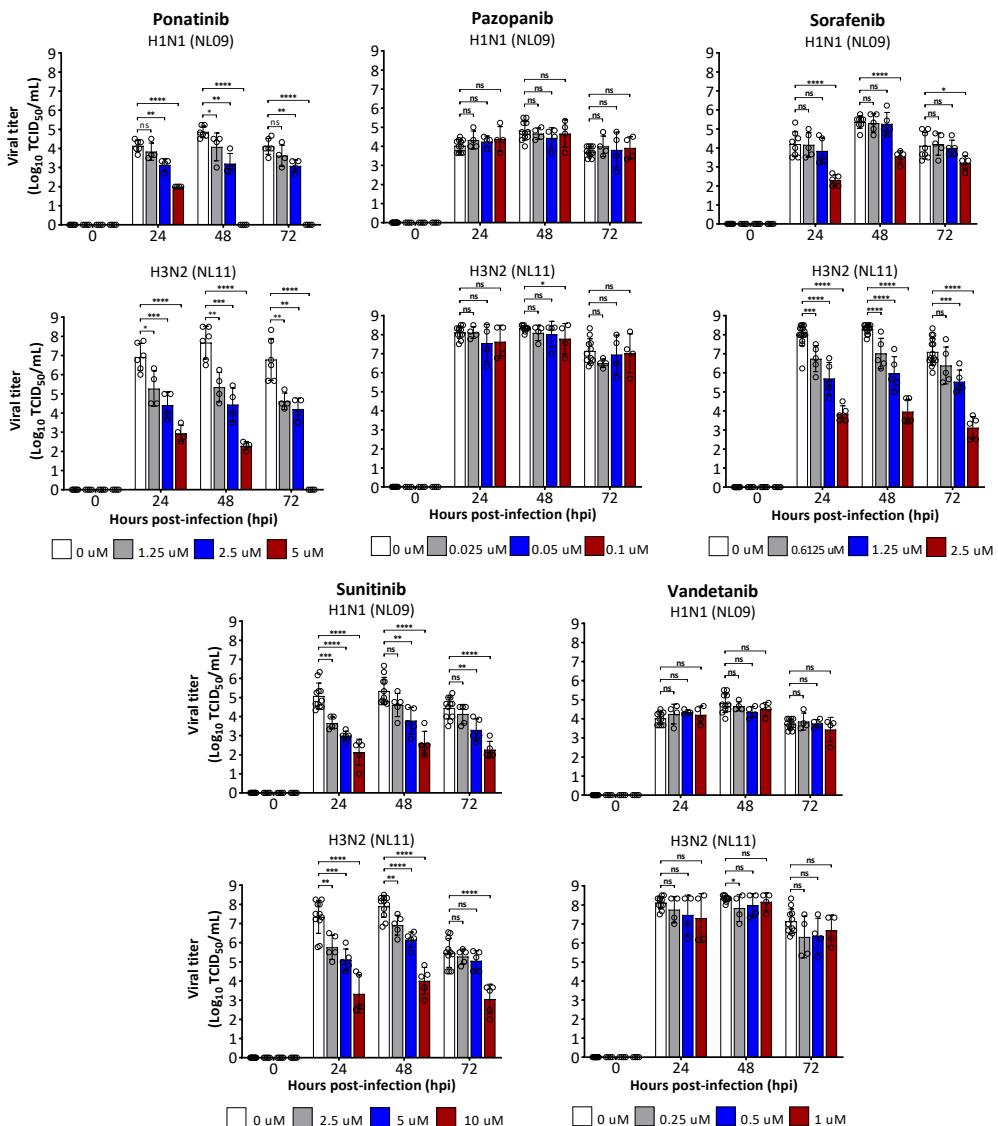
Hours post-infection (hpi)	0 μM	2.5 μM	5 μM	10 μM
0	~0.5	~0.5	~0.5	~0.5
24	~8.0	~8.0	~8.0	~8.0
48	~8.0	~7.5	~7.5	~7.5
72	~7.5	~6.0	~5.5	~5.5

Detailed description: This bar chart displays the HA titer of H3N2 (NL11) over a 72-hour period at four different inhibitor concentrations. The y-axis measures HA titer from 0 to 9. The x-axis shows time points at 0, 24, 48, and 72 hours post-infection (hpi). For each time point, four bars represent the concentrations: 0 μM (white), 2.5 μM (light gray), 5 μM (medium gray), and 10 μM (dark gray/red). Error bars indicate standard deviation. At 0 hpi, HA titers are near zero for all conditions. By 24 hpi, HA titers increase significantly, peaking around 7.5-8.0. At 48 hpi, the 0 μM group reaches the highest peak of approximately 8.5. As the inhibitor concentration increases, the HA titer decreases, with the 10 μM group reaching the lowest peak of about 6.5. At 72 hpi, the HA titers drop sharply across all groups, with the 10 μM group showing the most significant reduction.

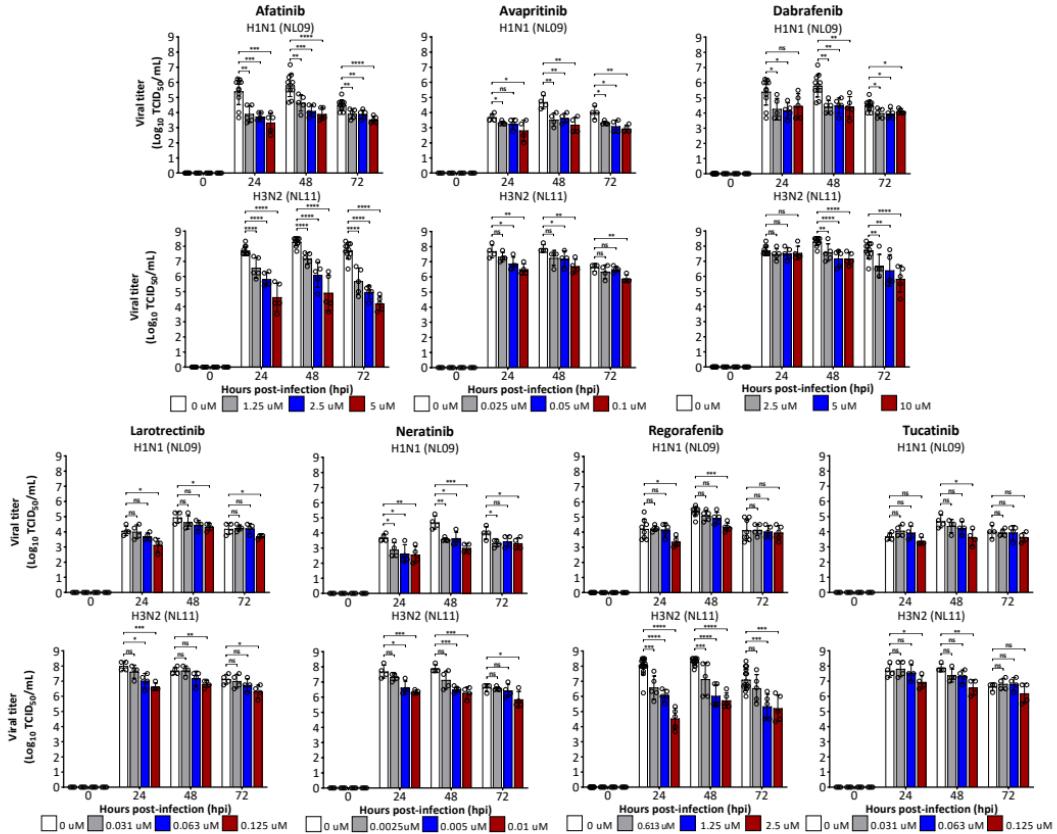
Hours post-infection (hpi)	0 μM	2.5 μM	5 μM	10 μM
0	~0.5	~0.5	~0.5	~0.5
24	~7.5	~7.8	~7.2	~6.8
48	~8.5	~7.8	~7.2	~6.5
72	~2.5	~3.5	~3.0	~2.5

Detailed description: A bar chart showing HA binding for H3N2 (NL11) at four time points: 0, 24, 48, and 72 hours post-infection. The y-axis represents HA binding, ranging from 0 to 100%. The x-axis shows concentrations: 0 uM (grey), 2.5 uM (blue), 5 uM (red), and 10 uM (black). Error bars represent standard deviation.

Hours post-infection	0 uM	2.5 uM	5 uM	10 uM
0	~100%	~100%	~100%	~100%
24	~100%	~100%	~100%	~100%
48	~100%	~100%	~100%	~100%
72	~100%	~100%	~100%	~100%

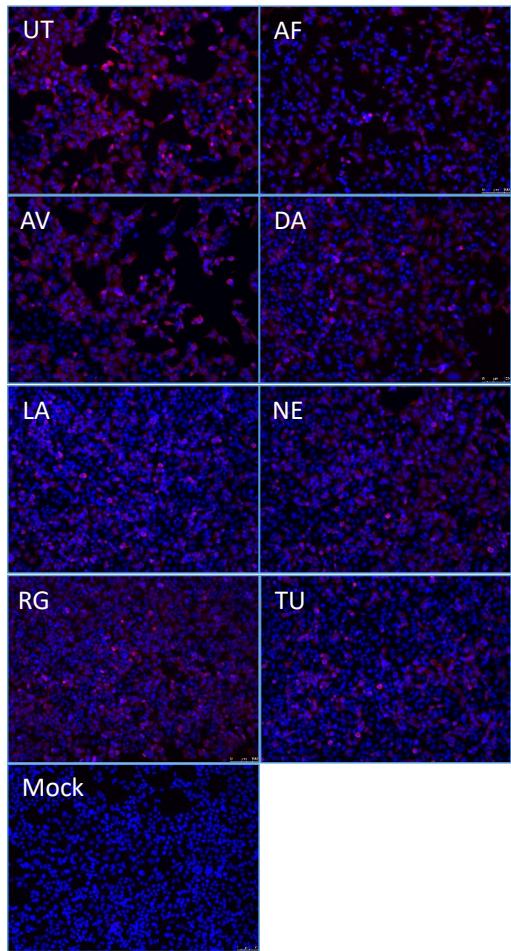


Supplemental Figure S1: SMKI candidate screening against NL09 and NL11 infections. A549 cells were infected with NL09 or NL11 at MOI=1 and incubated for 72h +/- indicated SMKIs at [0.25x, 0.5x or 1x]_{max} concentrations. At 24, 48, and 72 hpi, supernatants were collected, and viral titers quantified by TCID₅₀/ml assay (n = 4). Means \pm SD are shown. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001; ns, not significant (P>0.05).

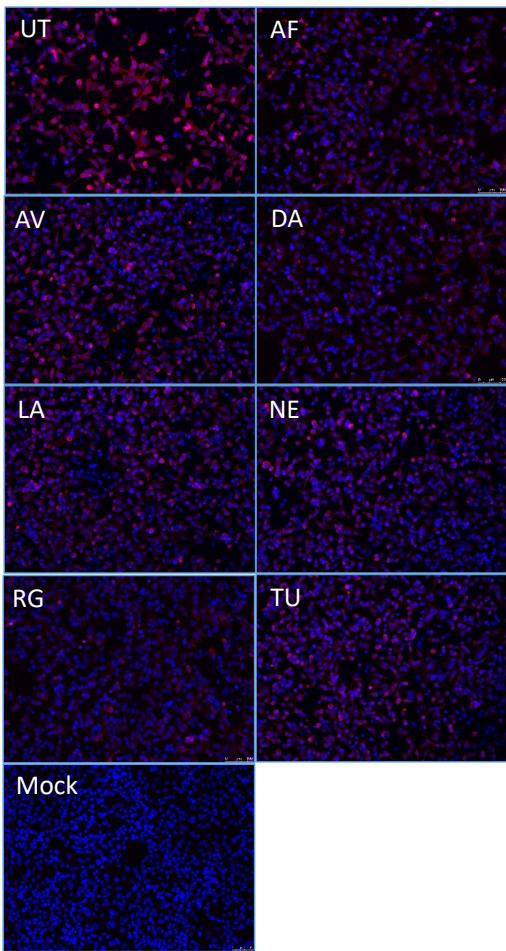


Supplemental Figure S2: Effect of Selected SMKI treatment on NL09 and NL11 infections. Related to Fig. 1B. A549 cells were infected with NL09 or NL11 at MOI=1 and incubated for 72h +/- indicated SMKIs at [0.25x, 0.5x or 1x]_{max} concentrations. At 24, 48, and 72 hpi, supernatants were collected, and viral titers quantified by TCID₅₀/ml assay (n = 4). Means \pm SD are shown. * P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001; ns, not significant (P>0.05).

NL09 (pH1N1)



NL11 (H3N2)



Supplemental Figure S3. Immunofluorescent detection of SMKIs' effects on cell viability and infectivity during infection. Related to Fig. 1C and 1D. A549 cells were infected with NL09 or NL11 at MOI=1 +/- indicated SMKIs at $[0.5x]_{\max}$ concentration for 48h. Fluorescence microscopy pictures were captured using a Leica DMI8 fluorescence microscope (representative field shown from an n=4/condition). Virus- infected cells were detected by anti-IAV NP antibody (red), and nuclei were detected using NucBlue Live ReadyProbes (blue).