Supplementary Materials

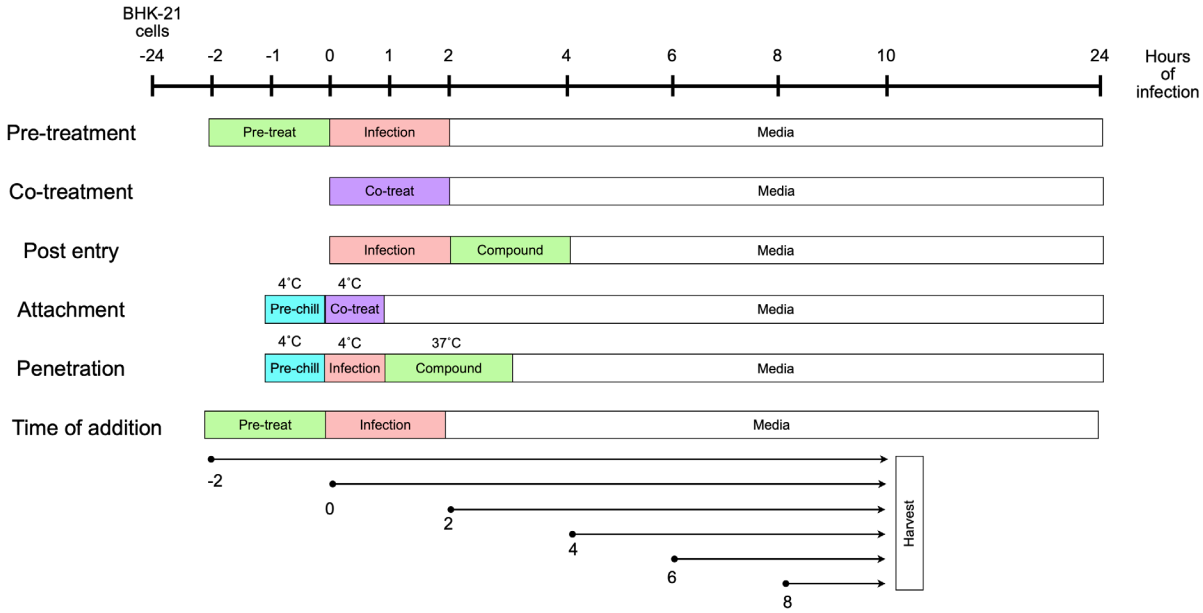

Figure S1. The experimental design of antiviral activity studies.

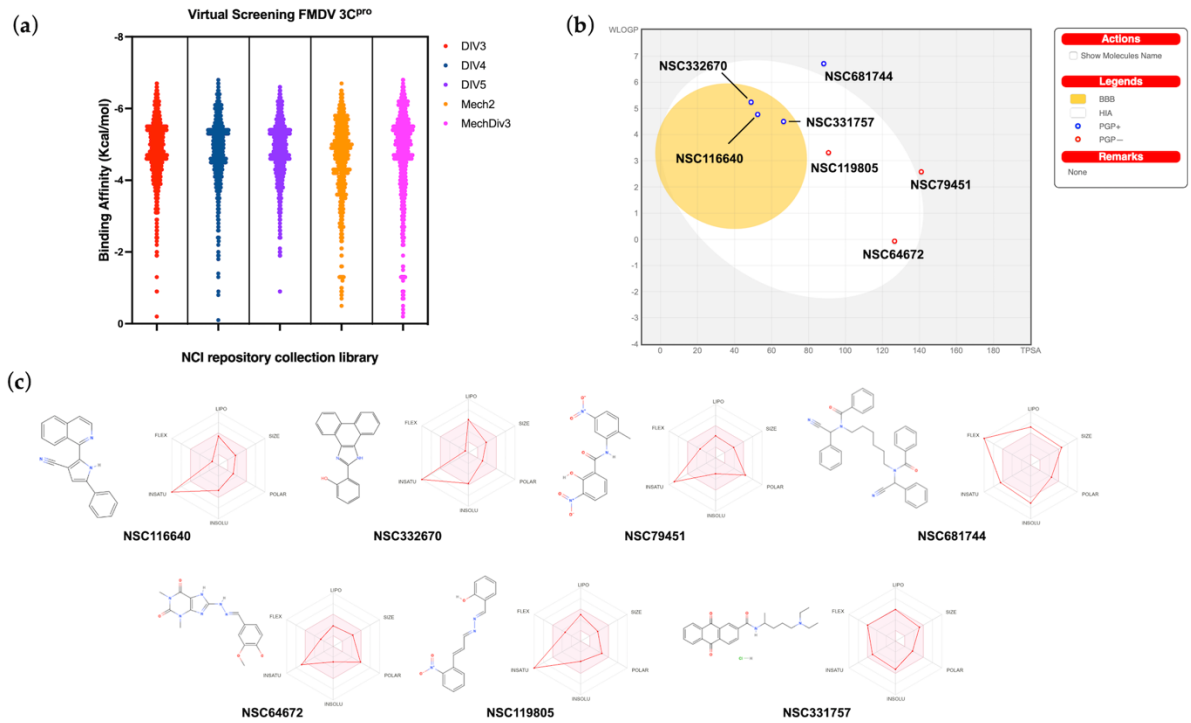

Figure S2. Structure-based virtual screening of NCI repository collection library. (**a**)The binding affinity of the compounds in each library. (**b**) The BOILED-Egg prediction of the compounds depicts the gastrointestinal absorption and brain penetration. BBB (yellow zone; blood-brain barrier) and HIA (white zone; human intestinal absorption). Blue dot (PGP+) and red dot (PGP–) represent positive and negative biochemical efflux (e.g., P-glycoprotein pumping out substrates from central nervous system (CNS)), respectively. (**c**) The initial hit compounds were selected for further cell-based assay, which the predicted physicochemical space presents the pink color zone as for oral bioavailability. LIPO (lopophility: -0.7 < XLOGP3 < +5.0; SIZE:1560g/mol < MV < 500g/mol; POLAR (polarity): 20Å^2 < TPSA < 130 Å^2; INSOLU (insolubility): -6 < LogS (ESOL) < 0; INSATU (instaturation): 0.25 < Fraction Csp3 < 1; FLEX (flexibility): 0 < Number rotatable bonds < 9.

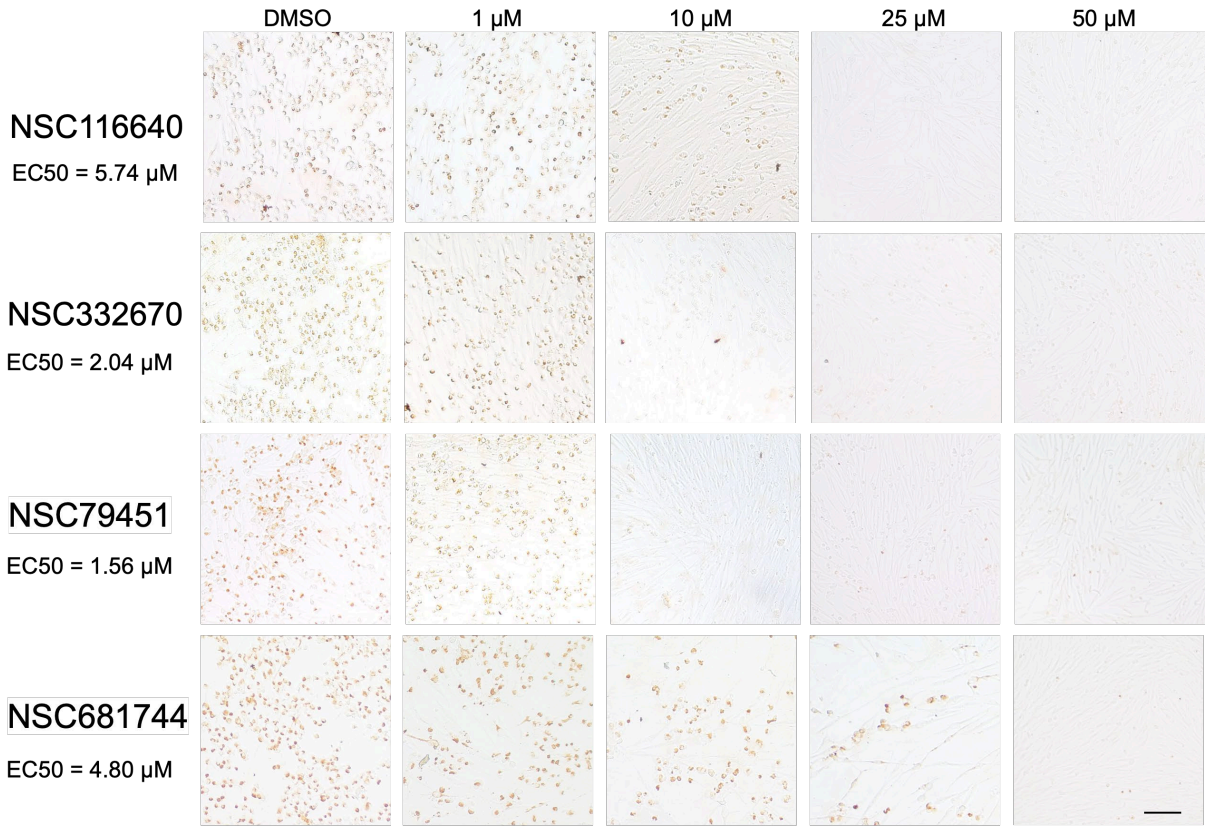

Figure S3. The antiviral activity of co-treatment assay which the serially diluted compounds were co-incubated with FMDV (10 TCID50/well). Scale bar is 100 μM.

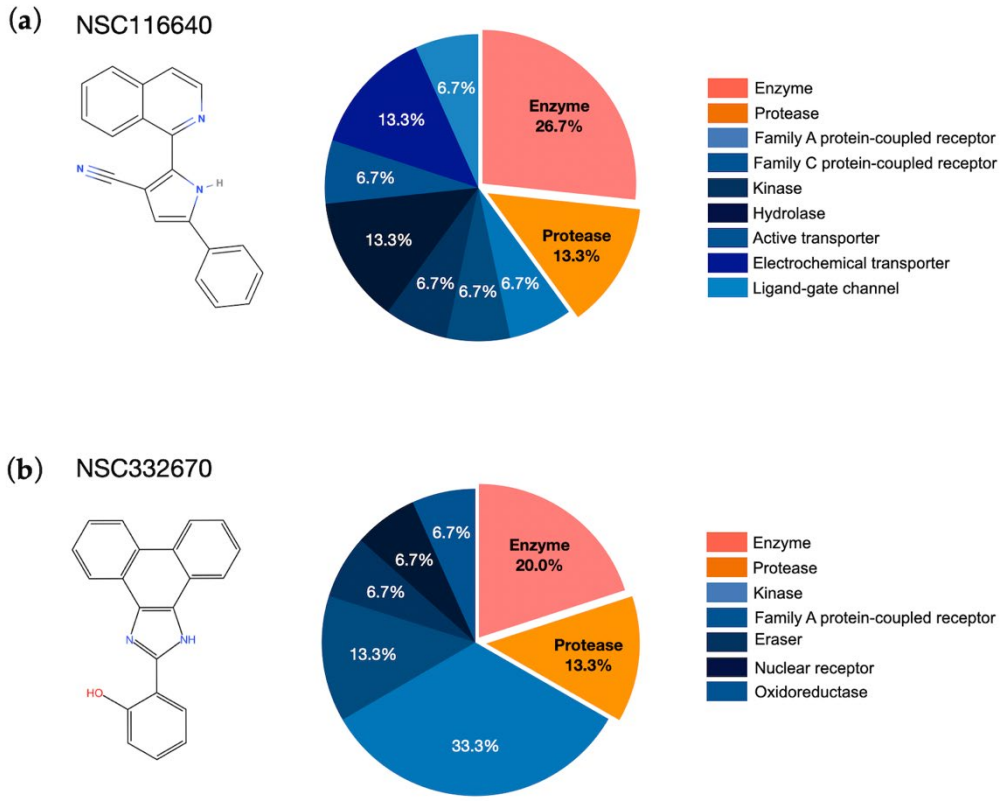

Figure S4. Target prediction of compounds (**a**) NSC116640 and (**b**) NSC332670.