Novel inhibitors of Foot and Mouth Disease Virus (FMDV) Targeting the RNA-Dependent RNA Polymerase activity of 3Dpol

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Foot-and-Mouth Disease Virus (FMDV) is a positive stranded picornavirus which infects cloven-hoofed animals, such as cattle, pigs and sheep, and leads to severe losses in livestock production. In the case of an FMD outbreak, emergency vaccination could be used but it would require at least 7 days to trigger an effective immune response. On the contrary, the use of antiviral drugs is expected to have prophylactic and/or therapeutic effects almost immediately. However, there are currently no approved FMDV inhibitors. Here we have applied a combination of screening, biochemical, virological, and molecular modeling tools to discover, validate, and characterize novel inhibitors of FMDV replication. Using a luciferase-based assay we have screened a chemical library of compounds and have identified two compounds, 5-chloro-3-(thiophen-2-yl-sulfanylmethyl)-1-benzothiophene 1,1-dioxide (or C7F8) and N'1-thieno[2,3-d]pyrimidin-4-yl-4-chloro-1-benzenesulfonohydrazide (or C5D9) that inhibited the RNA-dependent RNA polymerase activity of FMDV replicase (3Dpol) with IC_{50} values of 2.5 μM and 15 μM respectively. These compounds were shown to be specific inhibitors of FMDV 3Dpol and not nucleic acid chelators, as they did not affect activity of other viral polymerases using the same nucleic acid substrate. Molecular modeling docking experiments suggest that both inhibitors bind at a pocket proximal to, but distinct from, the NTP binding site of 3Dpol, thereby affecting indirectly RNA synthesis. C7F8 and C5d9 were not cytotoxic at concentrations up to at least 100 □M. Importantly, C5D9 exhibited antiviral activity and suppressed virus production in FMDV-infected cells with 50% and 90% effective concentrations (EC_{50} and EC_{90}) of 10 □M and 20 □M, respectively. The results indicate that 3Dpol inhibitors can be promising anti-FMDV agents for use as alternative or supplementary options to contain future outbreaks of FMD.