ABSTRACT

The influenza virus, a member of the *Orthomyxoviridae* family, plays a pivotal role in the occurrence of yearly respiratory epidemics and sporadic pandemics. Influenza accounts for an estimated 290,000 – 650,000 deaths worldwide each year. Both swine and avian hosts can act as reservoirs for influenza A virus, with interspecies transmission sometimes leading to global pandemics, such as the 2009 H1N1 swine flu pandemic.

However, despite the availability of antiviral drugs such as Tamiflu®, Xofluza®, and Relenza®, the efficacy of these treatments has been increasingly undermined by the emergence of drug-resistant strains. These antivirotics often face resistance issues and generally have only a moderate effect on alleviating the severity of symptoms. The persistent challenge of drug resistance highlights the critical need for ongoing research and the development of more effective influenza treatments.

The main objective of this Thesis is the design and synthesis of novel inhibitors of influenza virus RNA-dependent RNA polymerase (RdRp). The main focus is on RdRp endonuclease inhibitors. This metalloenzyme contains an active site that binds Mg^{2+}/Mn^{2+} ions, which are essential for its endonuclease activity. Effective inhibitors must therefore effectively chelate these ions. Novel inhibitors described in this Thesis include compounds with a thiochromenone structural motif (**Figure 1A**), C-7 and C-8 substituted luteolin derivatives (**Figure 1B**,**C**), and compounds with a polyphenolic structure (**Figure 1D–F**).

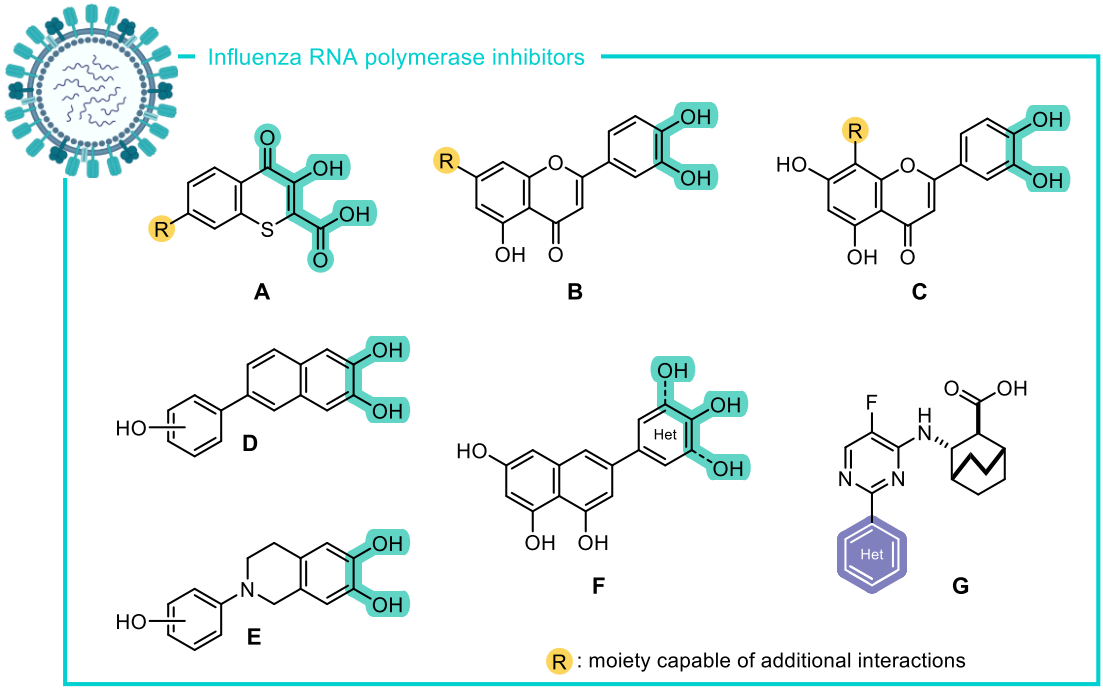

Figure 1 – **A–F)** Structures of potential influenza virus RdRp endonuclease inhibitors. Metal ion-coordinating fragments are highlighted in cyan. **G)** Structures of potential inhibitors of the PB2-subunit of RdRp.

Another objective of this work was to design and synthesize inhibitors targeting the PB2-subunit of the influenza virus RNA-dependent RNA polymerase (RdRp), utilizing a pyrimidine structural motif. (**Figure 1G**).

Finally, the aim of this work was to prepare the first ever inhibitors of orthonairoviruses from the *Bunyavirales* order, namely CCHFV and YEZV. As part of a hit-to-lead strategy, the chemical environment at the C-6 position of dihydroxypicolinic acid (**Figure 2H**) and the 5-hydroxy-4-pyrimidone at the C-2 position (**Figure 2I**) was investigated. Our approach led to the synthesis of extremely promising potential inhibitors of the endonucleases of the aforementioned orthonairoviruses. Thus, these compounds may provide the basis for future therapies for infections caused by these deadly viruses.

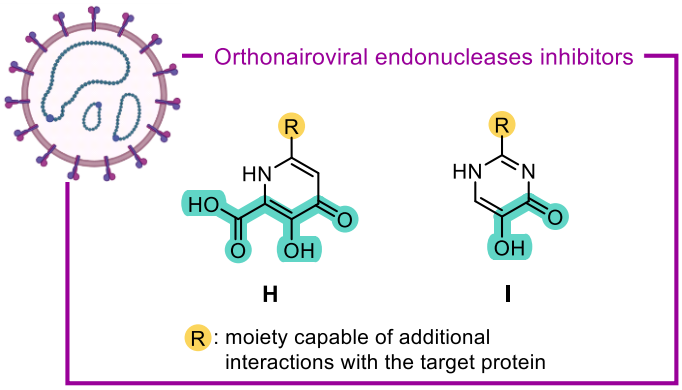

Figure 2 – H–I) Structures of potential L-protein endonuclease (RdRp) inhibitors of CCHFV and YEZV viruses of the *Bunyavirales* order. Metal ion-coordinating fragments are highlighted in cyan.

KEY WORDS

RNA polymerase, influenza virus, endonuclease, inhibitor, thiochromenone, flavonoids, PA subunit, PB2 subunit, CCHFV, YEZV, cross-coupling, C–H activation, prodrugs