**SUPPLEMENTARY MATERIAL**

# Semisynthetic cardenolides acting as antiviral inhibitors of influenza A virus replication by preventing polymerase complex formation

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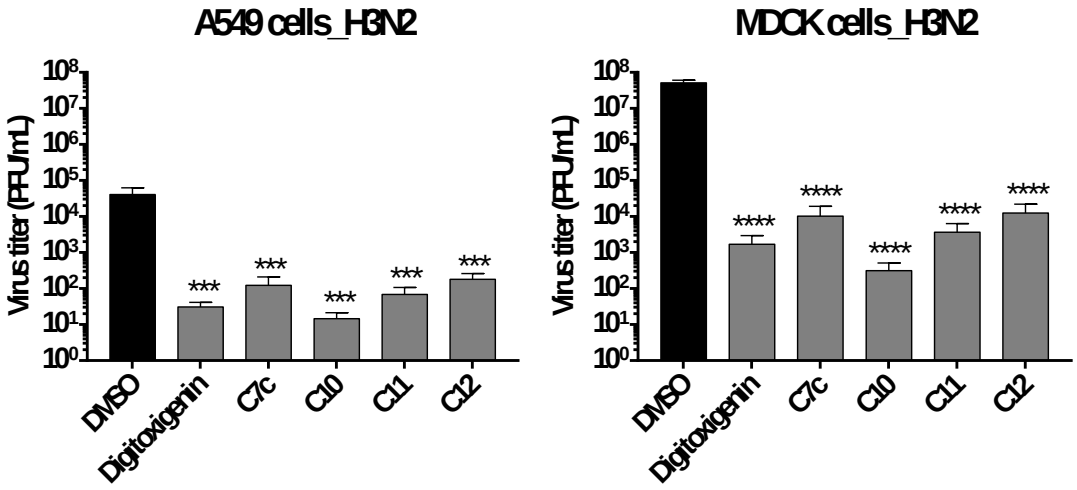
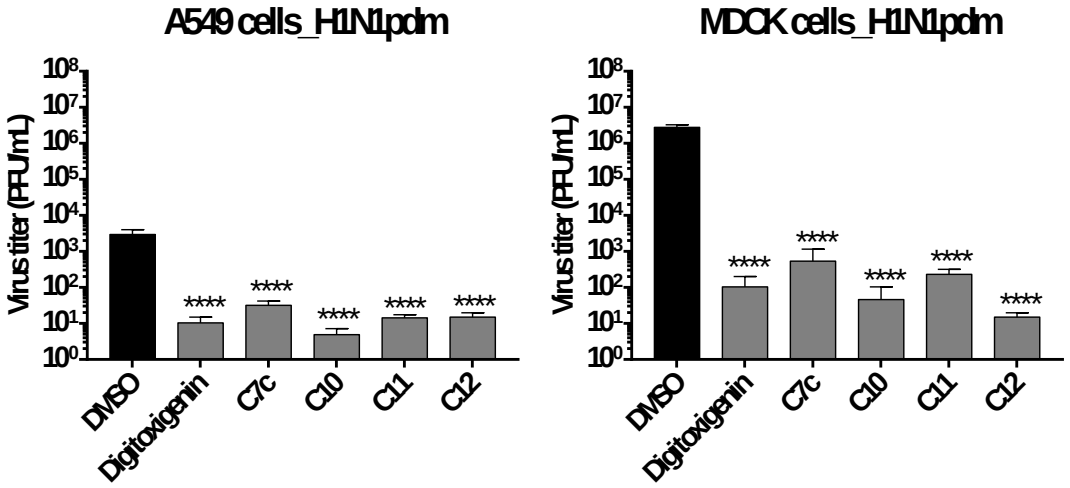
## Supplementary data index

**Fig. S1**. Antiviral activity of new cardenolide derivatives **C7c**, **C10**, **C11** and **C12** and digitoxigenin against distinct Influenza A and B Virus strains, at 1 µM. ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$ *vs* DMSO, one-way ANOVA, post-hoc test Dunnet.

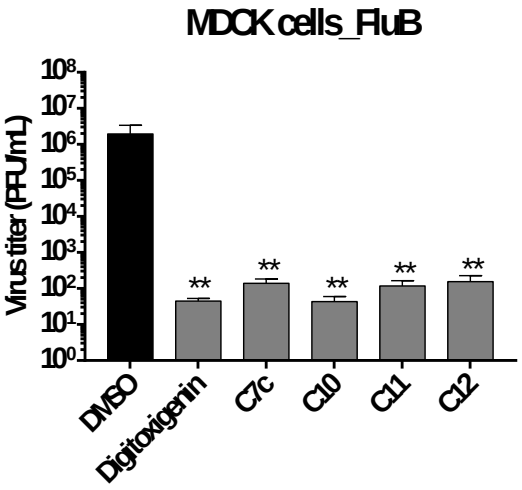
**A)** Influenza A Virus [Panama/2007/1999 (H3N2)] on A549 and MDCK cells.




**B)** Influenza A Virus [Hamburg/04/2009(H1N1pdm)] on A549 and MDCK cells.



**C)** Influenza B Virus (Lee/40) on MDCK cells.




**D)** Influenza A Virus [Seal/Mass/1-SC35M/80 (H7N7) (SC35M)] on A549 and MDCK cells.

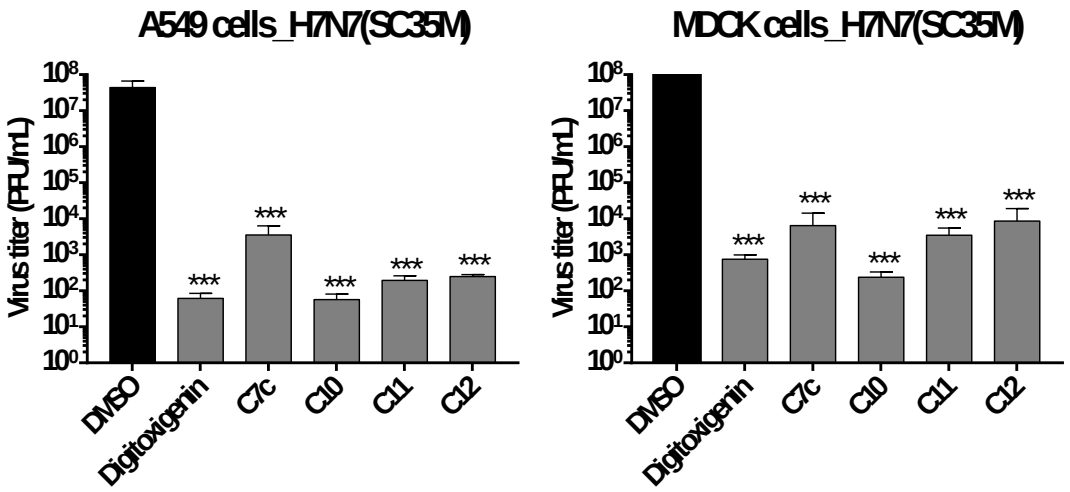


**Fig. S2**. Viability of human tumor-free lung explants after treatment with **C10** and **C11**. Lung tissue explants were treated and their viability over time was assessed by measuring LDH release in culture supernatants, which were collected at the indicated time points. Results are presented as Optical Densities at 450 nm and have been corrected according to the individual weights of the tissue fragments (mg). The experiment was repeated with lung tissues derived from four independent donors. Each time point represents mean (± SEM). DMSO served as solvent control. * p <0.05 *vs* MOCK, one-way ANOVA, post-hoc test Dunnet.