Identification of a new family of pyrimidine and pyridine derivatives as disruptors of the viral RNA-dependent RNA polymerase

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Influenza viruses are a class of RNA viruses which belongs to the *Orthomyxoviridae* family and includes four types, A, B, C and D. Among them, Influenza A virus is the most prevalent pathogen for both humans and animals, and it is responsible for the so-called seasonal flu, which affects millions of people every year with a significant economic impact. [1] RNA-dependent RNA polymerase (RdRp) recently emerged as a promising target for influenza therapy because of its key role in viral replication and its high conservation among viral strains. RdRp consists of three subunits, PA (polymerase acid protein), PB1 and PB2 (polymerase basic protein 1 and 2). Interestingly, the interaction between PA and PB1 subunits involves few amino acids and can be inhibited by small molecules. [2] We recently reported the 3-cyano-4,6-diphenylpyridine as a promising core to develop disruptors of PA-PB1 interactions. These studies led to the discovery of some derivatives endowed with low cytotoxicity and an interesting antiviral effect in cell assays. [3,4]

Herein, we report the synthesis and the biological evaluation of a new family of related compounds, in detail the 4,6-diphenylpyrimidine derivatives, in which the nitrogen of the cyano group in C3 has been included into the ring, and the simpler 4,6-diphenylpyridine isosters. This idea came from the knowledge that CN is often related to a potential cytotoxicity, and it is supported by molecular dynamic simulations which show that the removal of the CN group doesn't affect the key interactions between the compounds and PA subunit. [3] *In silico* studies, synthesis and antiviral activity of these derivatives will be reported in the poster session.

[1] http://www.who.int/influenza/en.
[2] Pflug A, *et al.*, *Nature* **2014;** 516(7531):355-60.
[3] Trist IML, *et al.*, *J Med Chem* **2016;** 59(6):2688-703.
[4] D'Agostino I, *et al.*, *Eur J Med Chem* **2018;** 157:743-58.