

*IX Giornate Italo-Francesi di Chimica*  
*IX Journées Franco-Italiennes de Chimie*  
 Genova  
 April 16-18, 2018

### 3-Cyano-4,6-diphenyl-pyridine amino acid derivatives active as influenza A polymerase inhibitors

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Influenza (Flu) is an infectious disease caused by negative-single-stranded and segmented RNA viruses, which belong to the *Orthomyxoviridae* family. These are classified in type A, B, C and D. Among them, influenza A virus (FluA) is responsible for the most important human pandemics of the last century and it is very difficult to prevent and to treat because of the high mutation rate and genomic reassortment. The RNA-dependent RNA polymerase (RdRp) is widely recognized as one of the more promising anti-flu target, since it has a critical role in FluA infection progression and possesses a high genomic sequence conservation. RdRp is constituted by three subunit: PA (polymerase acid protein), PB1 and PB2 (polymerase basic protein 1 and 2) [1]. Our group has already identified the 3-cyano-4,6-diphenyl-pyridine scaffold **1** (Figure) as an interesting disruptor of the PA-PB1 complex of RdRp, by mimicking the N-terminal portion of PB1 and the most important interactions with the C-terminal domain of PA [2,3]. Starting from this background, we decided to explore the chemical space around the C2 side chain of the pyridine scaffold, synthesizing derivatives **2a-p** (Figure). We introduced in C2 one, two or three amino acids as free acids or as esters, to ensure membrane permeability. The majority of the molecules are not cytotoxic ( $CC_{50}$  values  $>250 \mu\text{M}$ ) and some of them show a good antiviral activity. In particular, the most active derivative possesses an  $IC_{50}$  of  $36 \mu\text{M}$  and  $EC_{50}$  values of  $39 \mu\text{M}$  and  $53 \mu\text{M}$  in plaque reduction assay (PRA) and in minireplicon assay, respectively. Detailed biological data will be reported in the poster section.

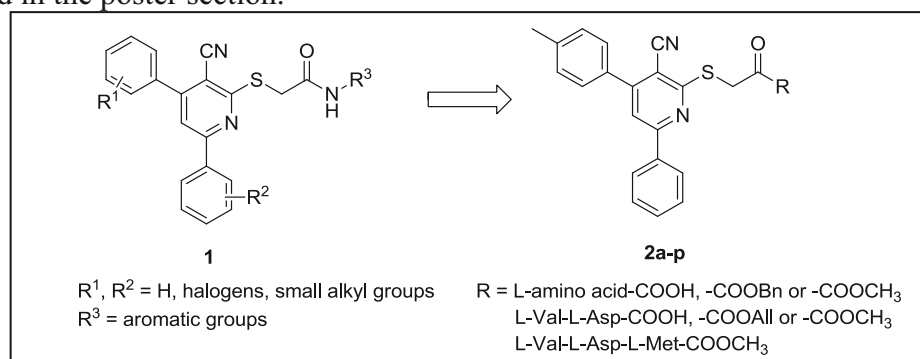


Figure: General structures of first (**1**) and second (**2**) generations of 3-cyano-4,6-diphenyl-pyridine derivatives

[1] Zhou, Z. *et al.* Drug Discovery Today (2018) [Epub ahead of print].

[2] Tintori, C. *et al.* Bioorg. Med. Chem. Lett. 24 (2014) 280-282.

[3] Trist, I. M. L. *et al.* J. Med. Chem. 69(6) (2016) 2688-703.

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