1,2,3-Triazolyl-4-oxoquinolines: a feasible beginning for promising chemical structures to inhibit Oseltamivir-resistant influenza A and B viruses

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Keywords: 1,2,3-triazole, 4-oxoquinoline, influenza viruses, neuraminidase inhibitors, oseltamivir carboxylate, antiviral resistance

Abstract

We described the synthesis of a series of 1,2,3-triazolyl-4-oxoquinolines and evaluated their ability to inhibit oseltamivir (OST)-resistant influenza strains.

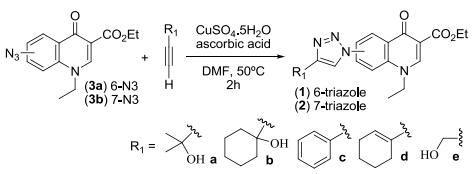
Introduction

Acute respiratory infections have a great impact on public health because they are a major cause of morbidity and mortality. Influenza virus, a negative-sense-RNA orthomixovirus, is the most important etiologic agent of severe acute respiratory infections (SARI). Influenza virus causes both seasonal infections and pandemic outbreaks. Thus, neuraminidase inhibitors (NAIs) such as oseltamivir (OST), zanamivir, peramivir and laninamivir constitute the only licensed class of drugs available for clinical use against influenza.

4-Oxoquinolones and triazolic derivatives have been largely explored due to multiple biological properties. They have been proven to be active against viruses such as HIV, HSV, HCV and influenza. In this work, we synthesized new 4-oxoquinoline derivatives **1a-e** and **2a-e** in which this core was connected to a 1,2,3-triazole nucleus and investigated their ability to inhibit influenza virus replication and the NA activity of OST-resistant strains of influenza.

Results and Discussion

The azido-4-oxoquinolines **3a** and **3b** allowed us to study their application in the Huisgen "click-chemistry" reaction using copper sulfate and ascorbic acid as the catalysts and dimethylformamide as the solvent at 50 ºC.



Scheme 1. Scheme summarizing the synthesis of 4-oxoquinolines **1a-e** e **2a-e**.

Compounds **1c** and **1d** were the most potent against the NA activity, reaching inhibitions equal to 89.0 and 94.8 %, respectively (OST=100 %).

Compound **1d** showed some advantages over OST in the inhibition of resistant strains of influenza. Although OST was more potent than compound **1d** in the inhibition of wild-type (WT) strains, compound **1d** IC_{50} values suffered only marginal changes in the presence of resistance mutations to OST.

Table 4. Potency against influenza replication and cytotoxicity of compound **1d**.

Compound	EC_{50} (μM)	CC_{50} (μM)	SI[a]
1d	0.20 ± 0.01	566 ± 89.5	2,830
Oseltamivir	0.03 ± 0.0023	321 ± 26	10,700

[a] SI, selective index is determined by the ratio between CC_{50} and EC_{50} values.

Compound **1d** was less cytotoxic than OST. Although OST' SI value is higher than the one observed for compound **2d**, our molecule is still very safe to be used *in vitro*.

Conclusions

Oxoquinoline derivative **1d** was the most potent compound within this series, inhibiting 94 % of WT influenza neuraminidase (NA) activity. Compound **1d** inhibited influenza virus replication with an EC_{50} of 0.2 μM with less cytotoxicity than OST, and also inhibited different OST-resistant NAs. These results suggest that 1,2,3-triazolyl-4-oxoquinolines represent promising lead molecules for further anti-influenza drug design.

Acknowledgements

The authors wish to thank CAPES, CNPq, FAPERJ and PPGQ-UFF.

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