



**Universiteit  
Leiden**  
The Netherlands

## **The quest for broad-spectrum coronavirus inhibitors**

Lima Leite Ogando, N.S.

### **Citation**

Lima Leite Ogando, N. S. (2021, October 12). *The quest for broad-spectrum coronavirus inhibitors*. Retrieved from <https://hdl.handle.net/1887/3217007>

Version: Not Applicable (or Unknown)

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3217007>

**Note:** To cite this publication please use the final published version (if applicable).

# **The quest for broad-spectrum coronavirus inhibitors**

Natacha Sofia Lima Leite Ogando

## **Colophon**

### **PhD Thesis, Leiden University, 2021**

- Thesis** The research described in this thesis was performed at Leiden University Medical Center, Department of Medical Microbiology, Leiden, The Netherlands
- Funding** The work presented in this thesis was supported by the Marie Skłodowska-Curie ETN European Training Network 'ANTIVIRALS' (EU grant agreement no. 642434), the SCORE project (EU Horizon 2020 program, grant agreement 101003627), and the #wakeuptocorona crowdfunding initiative of the Leiden University Fund (LUF) and LUMC Bontius Foundation.
- Layout** Natacha S. Ogando
- Cover** Natacha S. Ogando
- Print** Proefschriftmaken ([www.proefschriftmaken.nl](http://www.proefschriftmaken.nl))
- ISBN/EAN** 978-94-6423-444-2
- Copyright** ©2021, Natacha S. Ogando. All rights reserved. The copyright of the published articles has been transferred to the respective journals or publishers. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without prior permission of the author, the respective journal or publisher.

# The quest for broad-spectrum coronavirus inhibitors

## **Proefschrift**

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,  
op gezag van rector magnificus prof. dr. ir. H. Bijl,  
volgens besluit van het college voor promoties  
te verdedigen op dinsdag 12 oktober 2021  
klokke 15:00

door

**Natacha Sofia Lima Leite Ogando**

geboren te Sé Porto, Portugal

In 1988

**Promotor:** Prof. dr. E. J. Snijder

**Co-promotor:** Dr. C. C. Posthuma

**Leden van de promotiecommissie:**

Prof. dr. M. Roestenberg

Prof. dr. A.E. Gorbalenya

Prof. dr. F.J.M. van Kuppeveld (Universiteit Utrecht)

Prof. dr. B. Coutard (Universiteit van Aix-Marseille, Frankrijk)

*“We keep moving forward, opening new doors, and doing new things, because we’re curious  
and curiosity keeps leading us down new paths.”*

(Walt Disney; in the ending credits of the movie “Meet the Robinsons”, 2007)



## Table of contents

<b>Chapter 1</b>	General introduction and thesis outline	9
<b>Chapter 2</b>	SARS-coronavirus-2 replication in Vero E6 cells: replication kinetics, rapid adaptation and cytopathology	45
<b>Chapter 3</b>	The curious case of the nidovirus exoribonuclease: its role in RNA synthesis and replication fidelity	77
<b>Chapter 4</b>	The enzymatic activity of the nsp14 exoribonuclease is critical for replication of MERS-CoV and SARS-CoV-2	109
<b>Chapter 5</b>	Functional characterization of the <i>Betacoronavirus</i> nsp14 N7-guanine methyltransferase	149
<b>Chapter 6</b>	Characterization of 6',6'-difluoro-aristeromycin as a potent inhibitor of MERS-CoV replication	181
<b>Chapter 7</b>	The cyclophilin-dependent calcineurin inhibitor voclosporin inhibits SARS-CoV-2 replication in cell culture	205
<b>Chapter 8</b>	General Discussion	229
	Abbreviations	263
	English summary	267
	Dutch summary (Samenvatting)	270
	List of publications	273
	Curriculum Vitae	275



