



Universiteit
Leiden
The Netherlands

The road to Insurmountability: Novel avenues to better target CC Chemokine Receptors

Ortiz Zacarías, N.V.

Citation

Ortiz Zacarías, N. V. (2019, December 4). *The road to Insurmountability: Novel avenues to better target CC Chemokine Receptors*. Retrieved from <https://hdl.handle.net/1887/81379>

Version: Publisher's Version

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

Downloaded from: <https://hdl.handle.net/1887/81379>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/81379> holds various files of this Leiden University dissertation.

Author: Ortiz Zacarías, N.V.

Title: The road to Insurmountability: Novel avenues to better target CC Chemokine Receptors

Issue Date: 2019-12-04

The road to Insurmountability

***Novel avenues to better target
CC Chemokine Receptors***

by Natalia V. Ortiz Zacarías

The research described in this thesis was performed at the Division of Drug Discovery and Safety of the Leiden Academic Centre for Drug Research (LACDR), Leiden University (Leiden, The Netherlands).

Cover design: Iñaki Vicuña Contany

Thesis lay-out: Natalia V. Ortiz Zacarías

Printing: Ridderprint BV

ISBN: 978-94-6375-677-8

© Copyright, Natalia V. Ortiz Zacarías, 2019

All rights reserved. No part of this book may be reproduced in any form or by any means without permission of the author.

The road to Insurmountability

Novel avenues to better target CC Chemokine Receptors

PROEFSCHRIFT

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,

op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,

volgens besluit van het College voor Promoties

te verdedigen op 4 december 2019

klokke 11:15 uur

door

Natalia Veneranda Ortiz Zacarías

geboren te Monterrey, Nuevo León, Mexico

in 1987

Promotors:

Prof. dr. Ad IJzerman

Dr. Laura Heitman

Promotiecommissie:

Prof. dr. Hubertus Irth (voorzitter)

Prof. dr. Joke Bouwstra (secretaris)

Prof. dr. Mette Rosenkilde

Dr. Anna Junker

Dr. Maikel Wijtmans

Deep roots are not reached by the frost
J.R.R. Tolkien, The Fellowship of the Ring

To my family and friends:
the roots in my life

TABLE OF CONTENTS

Chapter 1	General Introduction	9
Chapter 2	Intracellular receptor modulation: Novel approach to target GPCRs	23
Chapter 3	Structure of CC Chemokine Receptor 2 with Orthosteric and Allosteric Antagonists	45
Chapter 4	Pyrrolone derivatives as intracellular allosteric modulators for chemokine receptors: Selective and dual-targeting inhibitors of CC Chemokine Receptors 1 and 2	71
Chapter 5	Synthesis and pharmacological evaluation of triazolopyrimidinone derivatives as noncompetitive, intracellular antagonists for CCR2/5 chemokine receptors	109
Chapter 6	Design and characterization of an intracellular covalent ligand for CC Chemokine Receptor 2 (CCR2)	153
Chapter 7	A novel CCR2 antagonist inhibits atherogenesis in apoE deficient mice by achieving high receptor occupancy	183
Chapter 8	Conclusions and Future Perspectives	211
	Summary	227
	Nederlandse Samenvatting	229
	Curriculum Vitae	232
	List of publications	233
	Acknowledgements	235

