



Universiteit
Leiden
The Netherlands

MAGL modulators: structure-guided optimisation and characterisation

Huizenga, M.C.W.

Citation

Huizenga, M. C. W. (2024, September 10). *MAGL modulators: structure-guided optimisation and characterisation*. Retrieved from <https://hdl.handle.net/1887/4082969>

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/1887/4082969>

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

MAGL modulators

Structure-guided optimisation and characterisation

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 10 september 2024
klokke 13:00 uur

door

Mirjam Cornelia Willemina Huizenga

geboren te Gouda

in 1996

Promotor: Prof. dr. M. van der Stelt

Co-promotor: Dr. A.P.A. Janssen
Dr. R.J.B.H.N. van den Berg

Promotiecommissie: Prof. dr. S.I van Kasteren
Prof. dr. M. Ubbink
Prof. dr. A. Perrakis
Netherlands Cancer Institute (NKI)
Prof. dr. L.H. Heitman
Leiden Academic Centre for Drug Research (LACDR)
Dr. M. Nazaré
Leibniz Forschungsinstitut für Molekulare Pharmakologie (FMP), Germany
Dr. F.J. Dekker
University of Groningen (RUG)

ISBN: 978-94-6506-166-5
Printing: Ridderprint
Cover designed with Fooocus

All rights reserved. No parts of this thesis may be reproduced in any manner or by any means without the prior written permission from the author.

Table of contents

Chapter 1	7
General introduction	
Chapter 2	21
Structure-based lead optimisation delivers a MAGL inhibitor with improved cellular target engagement	
Chapter 3	53
Physicochemical property-based optimisation of MAGL inhibitors	
Chapter 4	83
Discovery of MAGL inhibitors with favourable physiochemical properties and cellular target engagement	
Chapter 5	117
Selectivity and <i>in vitro</i> ADME profiling of spirocyclic aryl sulfoxide MAGL inhibitors	
Chapter 6	139
Discovery of first-in-class MAGL degraders	
Chapter 7	159
Summary and Future Prospects	
Samenvatting	175
List of Publications	184
Curriculum Vitae	185